vision and its disorders

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE - Public Health Service

Cover illustration is a sculptured head of an ancient Mesopotamian ruler (Akkadian, circa 2340–2180 B.C.). The eyes were inlaid with costly stones which have been gouged out.

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NINDB Monograph No. 4

vision and its disorders

Prepared for the National Institute of Neurological Diseases and Blindness
by the
Subcommittee on Vision and its Disorders,
National Advisory Neurological Diseases and Blindness Council

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS MONOGRAPHS

This publication is the fourth of a monograph series of neurological science contributions published by the National Institute of Neurological Diseases and Blindness. The series will include studies and research projects of members of the Institute as well as studies, research projects, reports of conferences, and investigations sponsored by the Institute and issued under the direction of the Editorial Committee of the NINDB. The monographs will present comprehensive and specialized reports dealing with neurological, sensory, and communication disorders which will contribute to progress in these fields. Single copies of monographs and other publications prepared under the auspices of this Institute are available upon request.

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Foreword

Vision plays a dominant role in human life. As man's most important link to the world around him, the visual process profoundly affects learning, thinking motivation, and human communication.

Yet many thousands of human beings are deprived of precious sight because of diseases and disorders of the eye. Although modern methods of early detection, diagnosis, and treatment of diseases are saving the sight of many people, too many others still become blind each year. In addition, thousands of persons are affected by varying degrees of ocular impairments which hinder personal convenience and prove highly costly.

In its research program to help combat the blinding diseases, the National Institute of Neurological Diseases and Blindness has endeavored to find answers to the major causes of blindness and visual disability and the best ways of attacking these problems. To spur accomplishment of this goal, the National Advisory Neurological Diseases and Blindness Council, in November 1964, established the Subcommittee on Vision and its Disorders. A primary task of this group of 10 experts was to evaluate the state of research in vision and its disorders and propose ways of overcoming the major origins of sight deprivation and visual impairments.

In November 1966 the Subcommittee completed its task. The Institute is indebted to members for their comprehensive report published in this monograph. As leaders of knowledge in their respective fields, they have made available to the Institute, and contributed to the professions directly involved in problems of the human eye, the benefits of their careful appraisal.

Research offers the greatest promise of answers to the still unsolved disorders of vision. Hopefully, this report will help generate the wider attention and activity required to speed the goals of eye research.

RICHARD L. MASLAND, M.D.,
Director, National Institute of Neurological Diseases and Blindness.

Preface

This volume represents the summed efforts of many dedicated individuals. As a representative of the Subcommittee, I would like to acknowledge the kind assistance rendered by some of them. Mr. Sheldon Novick, Miss Mary Wayne, and Mr. Lin Mattison edited the report, and offered valuable advice. Mrs. Kathleen Berman, Mrs. Joan Pintchuk, and Miss Robyn Knefel helped type the prepublication manuscripts. Miss Marilyn Harris prepared many of the illustrations. Considerable cooperation was also provided by the Washington University Department of Medical Illustration and the Barnes Hospital Printing Shop.

The Subcommittee wishes to extend special thanks to Drs. Thygeson, Keeney, Erdbrink, Grant, Ashcroft, and Harley, and to Father Carroll for their reports, which have been added to the collective Subcommittee efforts presented in this report. Thanks are also extended to the investigators who aided committee members in the preparation of their material.

Various members of the staff of the National Institute of Neurological Diseases and Blindness also provided valuable data and other assistance. Appreciation is expressed to them for their contribution of effort in the publication of this report.

I would also like to thank the publishers of the C. V. Mosby Co., Penguin Books, the Director General of Antiquities (Baghdad), American Educational Research Association, and others for their permission to quote from their publications, or to reproduce the necessary illustrations. The glossary, reproduced with the kind permission of Research to Prevent Blindness, Inc., was presented at a science writers seminar held November 6–9, 1965.

We believe that the delineation of research in vision and its disorders presented in the following pages, although necessarily limited by space, includes all important aspects of the problem.

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Chairman, Subcommittee on Vision
and Its Disorders.

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vision and its disorders

part I

This attractive woman's face was sculptured in ancient Mesopotamia (circa 3500–3000 B.C.). The eyebrows were originally decorated with lapis lazuli, and the eyes were inlaid with shell, and lapis lazuli or obsidian was used for the pupils.

Courtesy, Penguin Books, and the Director General of Antiquities, Baghdad, Iraq. This plate is reproduced from the book "The Art and Architecture of the Ancient Orient," by Henri Frankfort, publisher Penguin Books, Harmondsworth, Middlesex, England, 1954, plate 7.

Chapter I—INTRODUCTION

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SUBCOMMITTEE'S MAJOR PURPOSE AND EMPHASIS

The Subcommittee on Vision and Its Disorders, established as a task force by the National Advisory Neurological Diseases and Blindness Council, was asked to evaluate the state of research dealing with vision and its disorders, and to delineate areas requiring greater concentration and effort.

The Subcommittee finds that the national need for eye research is growing. Undersecretary of the Department of Health, Education, and Welfare, Wilbur C. Cohen, has noted an increase in blindness of 67 percent during 1940-60, a period in which U.S. population increased only 36 percent. The number of the blind in this country gives only a partial indication of the extent of damage done by visual disorders.

Throughout this report, emphasis is given to the hardships and costs created by blindness. This is, of course, the most serious damage within the scope of our considerations and, after cancer, the most feared affliction in this country. No single loss affects such a wide range of human activities. Even a brief consideration of a multitude of everyday tasks, from driving a car to reading a newspaper, to the demands of almost every kind of employment, gives a sense of how damaging such loss can be.

Costs to this Nation in suffering and loss of productivity from eye damage, short of blindness, are also commanding. In fact, in chapter 3 the Subcommittee points out that the economic costs of visual impairment are equivalent to those of blindness itself. Visual disorders, in fact, lie on a continuum from mild correctable disorders—requiring large numbers of our population to wear eye glasses at some time during their lives—to the terrible disability of blindness. Only a concerted research effort, simultaneously on many scientific fronts, will allow us to deal with the whole spectrum of visual diseases and anomalies. Our understanding of the eye and the visual system in its normal state must also be vastly advanced before added significant research breakthroughs can be made.

The Subcommittee is pleased to note that the current Nobel Prize for Medicine has been awarded to three outstanding visual scientists, G. Wald, K. Hartline, and R. Granit. When making their award, the Nobel Prize selection committee considers the ingenuity and competence of the investigator as well as the significance of the problem investigated.

Impressive progress is being made in a number of eye research fields. Some revolutionary discoveries have recently been reported, and in certain areas the Subcommittee expects similar progress in the near future—if adequate leadership, manpower, support, and facilities are available. In the final analysis we must build upon the talents of individual investigators. To attract high-caliber scientists and scientist-clinicians we must obtain the necessary salaries, provide job stability, and develop laboratories, supporting staff, and equipment.

In view of the enormous cost of blindness and visual impairment to the Nation and the excellent prospects for progress in the near future, we believe that the national research effort devoted to the eye and vision should be strengthened.

ORGANIZATION OF THE REPORT

Opening chapters of this report, part I, present a summary of research in vision and the magnitude of problems of the eye, including data on causes of visual impairments, prevalence, and costs. Technical reports presented in succeeding chapters, part II, will enable the reader to appreciate why and where reinforcement is needed in an attack on visual disorders. The subject of research in rehabilitation follows in part III. A glossary of technical terms, part IV, concludes the volume.

Following is a condensation of the more specialized papers that are presented in detail in part II, for those who want to study the problem in depth. The reader will find in these specialized chapters the necessary documentation and a more complete discussion of the problems briefly touched upon in part I.

Dr. Alpern's report on visual physiology underlines the interdisciplinary nature of our most recent advances in unveiling the basic processes that govern vision. The following chapters focus more spe-

cifically on the functions performed by particular portions of the eye and their characteristic disorders. Dr. Breinin's chapters on ocular motility and neuro-ophthalmology concentrate on the respective roles of the muscles and nerves in normal and abnormal vision. Dr. Smelser's discussion of the cornea and conjunctiva is followed by Dr. Thygeson's paper on trachoma, the most common serious affliction that attacks the outer parts of the eye and its surrounding tissue.

Drs. Becker and Kolker combine an account of the specific mechanisms and tissues involved in glaucoma with a consideration of the alternatives currently available in diagnosis and treatment. Dr. Kinsey's paper on the lens of the eye gives detailed consideration to its major disorder, cataract. Dr. Maumenee's chapter on uveitis focuses on the puzzling variety of blinding disorders that strike the eye's uveal tract.

Drs. Newell and Krill provide a comprehensive review of research on retinal diseases. Their paper is followed by two chapters analyzing the sources of its most common breakdowns. Drs. Leopold and Lieberman discuss the ocular effects of systemic diseases and emphasize the role of general vascular conditions in causing retinal damage and visual loss. Dr. Leopold's subsequent report enlarges on the theme by giving a detailed examination of diabetic retinopathy.

Dr. Zimmerman's chapter highlights the important issue of prenatal and developmental eye defects in infants. Then Drs. Lieberman and Leopold show how one such disease, retrolental fibroplasia, was conquered through research. In the following report on tumors of the eye, Dr. Zimmerman again points to the high toll of blinding diseases among children.

Eyes lost through accidents and poisonings are the focus of the next two chapters. Drs. Keeney and Erdbrink concentrate on the industrial and automotive aspects of the problem, while Dr. Grant discusses the specific ways in which the eye can be poisoned by direct contact with certain substances or systemically by absorbing drugs.

In Part III, Father Carroll examines the programs and prospects for rehabilitating all those who have suffered substantial visual impairment and blindness, whether from illness or accident. His report is supplemented by a review of research in the field by Ashcroft and Harley.

Chapter 2—A REVIEW OF RESEARCH IN VISION

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INTRODUCTION

True understanding of vision and visual problems would require competence in an enormous number of scientific disciplines. Here we have sought to summarize the major aspects of that body of knowledge and the status of current research in the field. Emphasis has been placed upon those aspects of the problem that are of particular interest to the National Institute of Neurological Diseases and Blindness, that is, research directed toward the optimal use of visual capabilities and the prevention of blinding diseases. Of course, it is difficult to define where the limits of our mandate fall, for an understanding of visual abnormalities can only be achieved when normal function has been defined. For example, one can comprehend anomalies in the chemistry of the light sensitive retinal receptor only if chemical reactions occurring in the normal receptor cell are already understood. Basic and clinical research are two faces of the same coin.

Through research directed toward the prevention and cure of blinding diseases, we can substantially reduce both the financial and human cost of visual impairment. No better example can be offered than our recent conquest of retrolental fibroplasia, a disease which was blinding 2,000 infants per year in the 1950's. This accomplishment has already saved between 10,000 to 20,000 children from a life handicapped by blindness. It will save the Nation an estimated $200 million every year in funds that would otherwise have had to be spent on their care and rehabilitation. Yet compared to the savings, the research investment was virtually insignificant.

In the last decade we have made a number of other important discoveries. The pigments responsible for color vision have been identified in single retinal receptors, and the causes of a number of color vision defects have been defined. Eye research had discovered a drug effective against the herpes simplex virus, one of the first pharmaceuticals found effective against any virus disease. In addition, we now have a working model which should help us understand the selective loss of vision and binocular function in children with cross-eyes and related problems.

Because children and older adults are the groups most afflicted, visual research largely concentrates on their problems. In the young, we seek to optimize visual capability. In the old, we try to sustain vision and extend the patient's productive life.

Each child whose vision is restored, sustained, or improved represents a gain for society. Human potential is enhanced, and the staggering cost of care, special training, and maintenance, which would otherwise be required throughout that individual's lifetime, is erased.

President Johnson recently called upon the research community to make a major effort to extend the prime of life for all Americans. It is difficult to keep up a useful, productive, and fruitful life in the presence of a major visual deficiency. Largely because of the rapid increase in the older age population, the number of blind and visually impaired among us is growing. Cataracts, glaucoma, senile macular degeneration, and diabetic retinopathy, are all predominantly diseases of old age and are all potentially blinding. These disorders take an increasing toll as medicine succeeds in extending longevity. In order to sustain the prime of life, we must seek means of preserving vision along with life itself.

Similarly, the President has called upon all of us to contribute to international health and welfare. The leading cause of blindness in the world today is trachoma, a disease affecting 400 million to 500 million people—one-seventh of mankind. Except among the American Indian population in the Southwest, we have eliminated this disease in the United States. Interestingly, the Peoples' Republic of China recently have made an exciting breakthrough in this field with the successful culture of the trachoma virus. The American ophthalmic research community can make a substantial contribution in helping to eradicate this disease and other afflictions throughout the world.

THE EYE

The eye is housed in a cone-shaped bony cavity known as the orbit. Through an opening at the rear

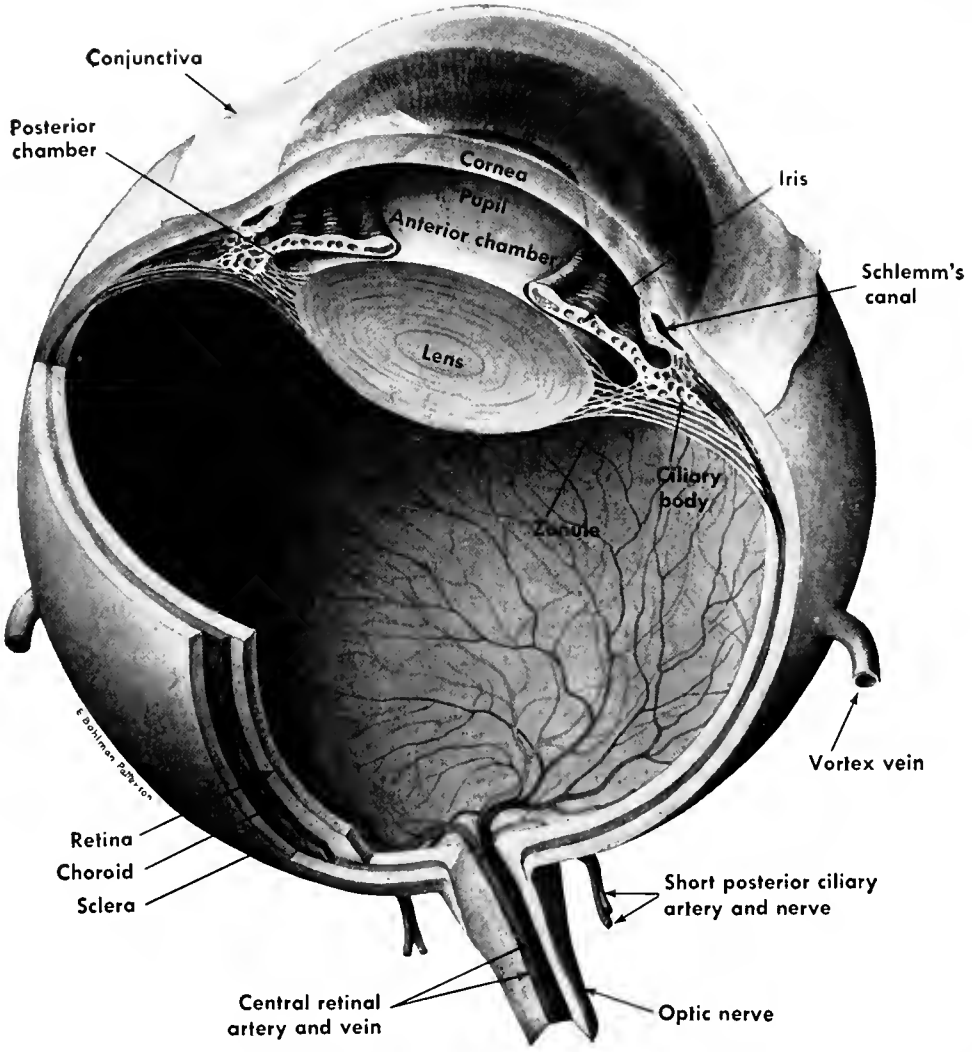

Figure 1.—The internal structures of the human eye. (This illustration is reproduced from Newell, F.: Ophthalmology, St. Louis, 1965, the C. V. Mosby Co.)

of the orbit the optic nerve passes from the eye to the brain. The movements of the eye are accomplished by the coordinated action of three pairs of muscles fastened to the outside surface of the globe (see fig. 2).

The eye is protected by the lids as well as by the bones of the orbit. Lining the inside of the lids and extending partially onto the front surface of the eye is a mucous membrane known as the conjunctiva. This membrane stops at the edge of the cornea, the transparent outer coat at the front of the eye. The cornea protects the internal structures of the eye, allows light to enter, and serves as the most powerful optical element of the eye. The cornea is continuous with the sclera which is the tough, white, outermost coat surrounding the remainder of the eye.

A small chamber, which is constantly filled with a circulating clear fluid known as the aqueous humor, is located behind the cornea. The aqueous carries nutrients to the various tissues at the front part of the eye which do not have their own blood supply. It is important to realize that if the cornea and the lens of the eye had a blood supply they could not maintain their transparency. At the rear of the aqueous chamber lies the colored iris which may be compared to the diaphragm of a camera, since it opens and closes according to the amount of light present. The pupil, which appears black, is the open space in the center of the iris.

The transparent lens of the eye lies just behind the pupil and is held in place by fine fibers known as zonules. The lens helps to focus the light to form a sharp image on the retina. When one changes from distant to near vision, the lens alters its shape, and

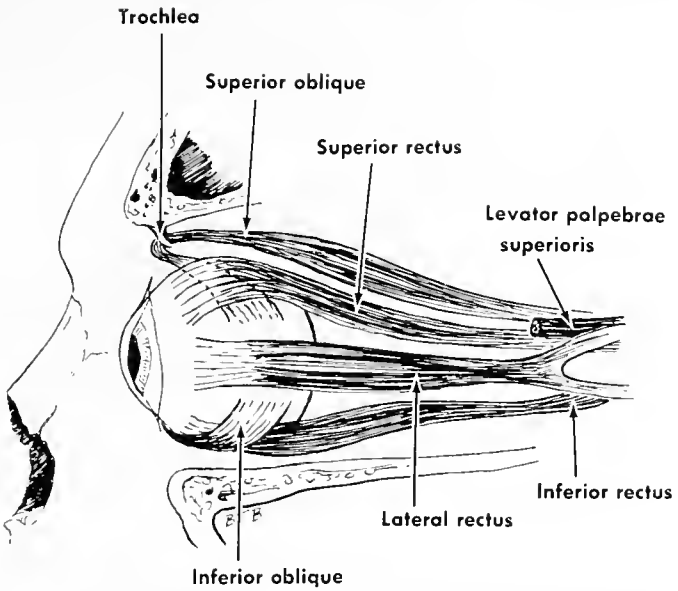

Figure 2.—The eye is shown within the orbit. The extrinsic (external) muscles of the eye insert into the sclera at different points, and rotate the eye when the individual gazes in different directions. The levator muscle (which has been cut in this drawing) raises the upper lid. (Reproduced from Newell, F.: Ophthalmology, St. Louis, 1965, the C. V. Mosby Co.)

hence its optical power; this change is known as accommodation. With increasing age we lose the ability to accommodate and require reading glasses or bifocals to assist us when looking at objects nearby.

Muscles in the ciliary body control lens power by varying tension on the zonules. This mechanism, combined with the elastic properties of the lens, serves to vary the optical strength of the lens.

The ciliary body is the peripheral continuation of the iris and produces the aqueous humor. The aqueous passes from the posterior chamber (which lies between the iris and the lens, fig. 3), into the anterior chamber and leaves the eye via outflow channels known as the trabecular meshwork. These channels are located near the junction of the iris and the cornea. After passing through the trabecular meshwork, the aqueous enters the bloodstream via numerous small veins in the white sclera. Excessive aqueous production and/or impairment of its flow out of the eye leads to elevation of the fluid pressure in the eye, which causes the disease glaucoma.

Behind the lens is a large cavity which contains a clear, gelatinous substance known as vitreous. Among other functions, the vitreous helps to maintain the shape of the eye.

The innermost layer at the back of the eye is the retina, which consists of several different highly complex cell layers. The retina, analogous to the film in a camera, is a specialized type of nervous tissue similar to, and derived from, brain tissue. It is sensitive to light and is able to translate information contained in images focused on the retina into nerve impulses. These impulses are sent via the optic nerve to the brain, where the neural excitation is interpreted, and we experience sight.

The choroid lies between the retina and the sclera, at the back of the eye (fig. 1). This layer is continuous with the ciliary body and iris and is very rich in blood vessels. The choroid provides nutrients for the retinal light receptors and other portions of the eye, and contains a light-absorbing dark pigment.

The central retinal artery and vein are two important blood vessels which travel along the optic nerve and directly supply the retina.

VISUAL PHYSIOLOGY AND REFRACTIVE ANOMALIES

The visual system is the most important point of contact between man and his surroundings. The whole sequence of events, from the instant that light hits the eye to the conscious reaction to the visual stimulus, has challenged investigators since the days of antiquity.

An understanding of visual physiology is fundamental for the advance of clinical practice not only in the eye care field, but also in several other specialty areas. Research concerned with the nature of visual excitation; with coding and decoding of nerve impulse signals from the eye to the brain; and with the nature of form, brightness, and color perception provides equally valuable information to the neurologist, the neurosurgeon, the psychiatrist, and the psychologist.

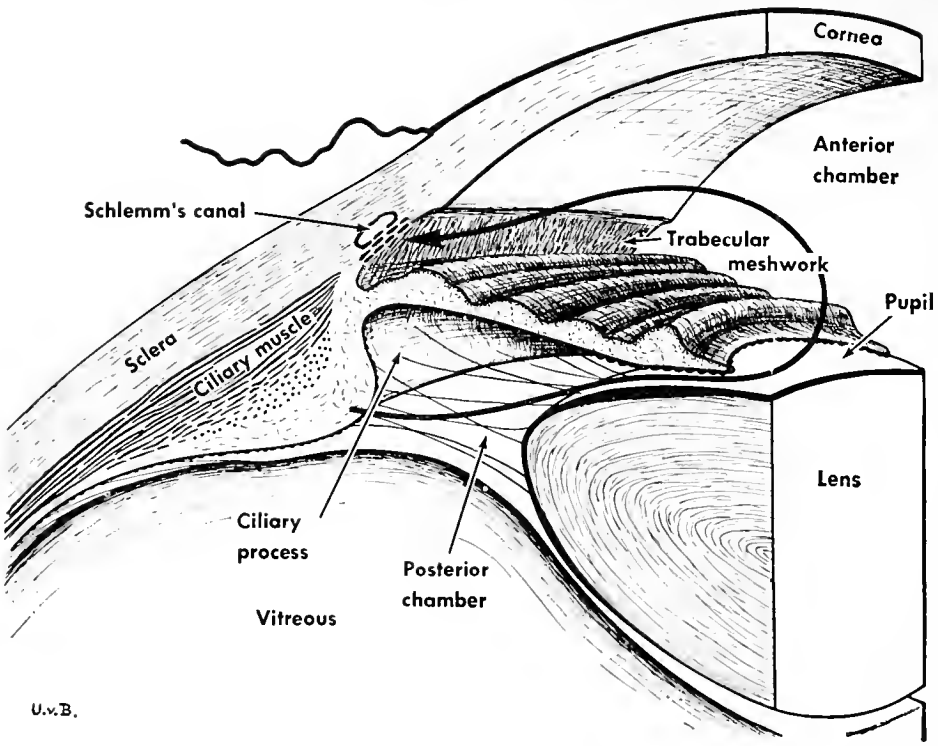

Figure 3.—This drawing illustrates the path of flow of the aqueous humor. It is formed by the ciliary body, enters the posterior chamber, passes into the anterior chamber through the pupil, and leaves the eye via the trabecular meshwork and Schlemm's canal. (Reproduced from Newell, F.: Ophthalmology, St. Louis, 1965, the C. V. Mosby Co.)

Advanced experimental models are being applied to many visual problems in our quest to understand the functioning of the visual system. For example, feedback control systems analysis is used in evaluating the coordinated movements of the eyes and in studies of the changes which occur when the eye shifts its focus. The same experimental designs are being applied to the reactions of the iris. Transfer functions allow us to relate the optical characteristics of the eye to those of optical instruments. This form of analysis can be extended to include certain visual responses. Information theory and neural-net concepts are valuable in our attempts to understand how the retina utilizes the content of the image falling on its surface.

Optical Errors of the Eye (Refractive Anomalies)

The amount of information which the nervous system can glean from the retinal image is dependent in part upon the quality of the optical system of the eye. That optical system is less than perfect, and in certain pathologic conditions there is a further decrease in retinal image quality. It is possible to correct defects in vision by a number of methods. Eye glasses, contact lenses, subnormal vision aids (telescopic lenses, simple microscopes, etc.), and corneal transplant, cataract, and intravitreal surgery are methods available for improving the quality of the retinal image. The surgical techniques are designed to remove (and, in some instances, to substitute for) irregular optical surfaces or normally transparent parts of the eye which have become cloudy or opaque.

Clear, distinct vision is essential in school, at work, and in pursuit of any number of worthwhile activities. A large percentage of our population requires eye glasses for optimal vision from childhood through senescence, yet a conflict of views persists regarding the nature and cause of the refractive anomalies—nearsightedness (myopia), farsightedness (hyperopia), etc. We know that many of these problems are in some manner genetically determined, but the mechanisms which, for example, cause a child to become nearsighted between the ages of seven and nine, and then progress to maximum nearsightedness during the teens, are far from understood. The degenerative changes which ultimately occur to produce blindness in the advanced years of the very myopic individual might be prevented if the processes which cause this form of myopia during the early years were defined and the process thwarted. High myopia remains a major cause of blindness and severe visual impairment.

New experimental procedures have been developed which should allow more penetrating study of various aspects of these problems. Infrared measuring devices, ultrasound, X-rays, and optical lasers have all been successfully employed. Broadly based epidemiological and genetic studies are needed, as well as physical and chemical analyses of eye bank eyes which had significant refractive anomalies. Recent surgical approaches and other remedies require continued careful evaluation. Improved contact lens fitting procedures are necessary for patients with irregular or scarred corneas. We believe that research on problems so universally applicable and important should be more actively pursued.

Visual Physiology

The image on the retina is composed of a distribution of light energy. The visual process is initiated by the light acting on photosensitive pigments contained in the individual retinal receptors. Many advances have been made in our understanding of the chemistry of these light sensitive visual pigments. The visual pigment molecule appears to have two parts, a light sensitive chromophore which is related to vitamin A, and a protein (which is less well understood).

Based on laborious psychophysical experiments first conducted a century ago, scientists concluded that in order for us to see color, there had to be at least three different light sensitive pigments in color sensitive retinal receptors. This deduction recently was confirmed experimentally. Three pigments have been identified in human eyes, and we believe that each retinal color vision receptor contains only one of these photosensitive pigments. This exciting discovery aids us in understanding a number of the defects in color vision which occur in about 8 percent of the male population, and in a far smaller number of females.

Although the initial photochemical processes occurring in the retinal receptors have been largely worked out, we still do not know how these biochemical reactions are translated into the nerve signals which are channeled to the brain. It will be important to define the mechanisms which control retinal sensitivity. Similarly, we must determine how the retina extracts information from the continually changing distribution of light energy falling on its surface. In studies directed toward the solution of these complex problems many investigators use primitive invertebrates, such as the horseshoe crab. These animals serve as simplified models of the more complex human retina.

Electrophysiology has come to play a major role in our attempts to understand the physiologic mechanisms of the eye and in our efforts to diagnose various diseases of the eyes and visual pathways. The electroretinogram, or ERG, is a measure of the changes in electrical potential which occur in the retina following exposure to light. Since a number of diseases of the retina and the choroid alter the electroretinogram, the ERG can be of considerable diagnostic value. It is an important tool in the evaluation of retinal function in infants and in those with whom we cannot effectively communicate; it is valuable when we wish to establish the quality of retinal function in patients with cloudy corneas and lenses; and it is useful in the early diagnosis of some inherited retinal diseases. Different defects, drugs, and various agents selectively affect the components of the ERG wave form.

Until recently, the ERG could only be used to show the mass response of the entire retina, and discrete areas could not be studied. However, special computers now allow us to identify localized ERG responses. These new techniques enhance investigations of the basic physiological processes of the human retina, and allow us better to evaluate response characteristics in retinal areas where discrete lesions are present or suspected. Computer techniques are also being applied to the analysis of visually excited potentials recorded from scalp electrodes placed over the brain.

It appears that much of the coding of the visual stimulus takes place in the retina. In fact, the eye appears to speak to the brain in a well organized language. Only recently have we begun to understand these complex processes. They will be important in the development of future differential diagnostic methods; for once we know the coding system, we will gain insight into the sort of functions which can be disrupted by visual disorders.

The advent of microelectrophysiological techniques has allowed us to study responses to light stimulation of single cells located along the visual pathways. For example, we are making progress in the definition of the role played by the lateral geniculate body, the way station at the base of the brain where fibers having origin in the optic nerve terminate. From there impulses pass to the cortex of the brain. Impulses from the two eyes first converge at the lateral geniculate body. There we have found a number of cells which respond to different stimuli; some are sensitive to changes in light intensity, others respond selectively to the color of the stimulus, and still others react only when the stimulus is moved. Truly exciting data are being obtained by a number of investigators who are conducting similar studies in the brain cortex. These studies should provide much information concerning central nervous system coding and data processing, and aid in defining the processes making vision possible.

Experimental psychologists using psychophysical techniques have been able to deduce how the visual

system handles many different stimuli. Using precisely calibrated visual test targets, they carefully studied responses of man and animals. Many of the characteristics of color vision, the recognition of objects, the sensing of flickering stimuli, etc., have been defined, although we still do not understand the physiological nature of these phenomena. Until recently, psychophysics was virtually the only available method for the study of visual physiology. That work has provided the solid foundation upon which recently developed biochemical and electrophysiological experimental designs have been built. Local events occurring in the visual system (defined by cell and molecular biology) can only be understood against a background of knowledge concerning the response characteristics of the visual system as a whole (provided by psychophysics).

OCULAR MOTILITY

In order to see a single image, the brain must accurately adjust the tone of twelve muscles, six controlling the orientation of each eye; it must also combine the incoming images from the two retinas, each of which looks at the world from a slightly different vantage point. This incredibly complex task of providing single, clear, binocular vision is subject to disruption from any of a number of causes. Certain types of refractive (optical) error, differences in the correction required in the left and right eyes, small discrepancies in the retinal image size in the two eyes, and so on, can lead to breakdowns in the binocular visual system—suppression of vision, reduced visual acuity or amblyopia, and strabismus (in popular terms, "cross-eyes" or "wall-eyes"). These common problems usually occur early in life, are extremely difficult to treat, and cause substantial social and economic problems for these children as they grow up.

Between 2 and 5 percent of our population (4 to 10 million Americans) do not have normal binocular vision, and 1 to 4 percent have amblyopia, that is, lack the ability to see clearly with one eye. Amblyopia becomes a serious handicap if the remaining good eye is covered temporarily, or injured, or diseased permanently.

Our knowledge is limited as to why the eyes turn in or out in strabismus, how amblyopia develops, and how to overcome amblyopia and restore useful vision. Binocular vision and the cerebral processes which mediate it are still a long way from being understood.

By stimulating specific areas in the brains of laboratory animals and observing their responses, we have learned that extremely complex systems govern the various types of eye movement. The fine structure, innervation, chemistry, and response characteristics of the muscles which control eye movements must be studied in detail, so that diseases which affect the ocular muscles may be better understood. Two different types of muscle fibers have been defined. It has been suggested that one type specializes in turning the eyes from side to side, while the second type serves to converge the eyes when we view near objects.

The ability to fuse the two images falling on the two retinas into one, and the perceptual processes and reflexes which maintain that fusion under different conditions of viewing, are skills which need to be better defined. The problem of how and to what degree fusion can be trained in cases of misalignment of the two eyes has not yet been adequately studied. The clinical science of orthoptics, which uses eye exercises and visual training in an attempt to restore or improve binocular (both eyes) and monocular (one eye) visual skills, does so largely on an empirical basis, with only limited physiological insight. The basic concepts upon which current clinical techniques are based require critical evaluation. This is an area requiring cooperative investigations by highly trained psychologists, neurophysiologists, and clinicians.

There is an apparent neural linkage between focusing and converging the eyes on a near object so that a single, clear picture derived from the two retinal images emerges. However, the exact stimulus or stimuli which induce the eyes to change their focus is unknown. Is it awareness or nearness, or some aspect of the blurred retinal image? It is important to study the relationships between these functions and the effect of one upon the other—particularly if we are to develop an understanding of that form of strabismus known as accommodative esotropia, which is common in the farsighted child. These same relationships underlie many of the problems resulting in "eye strain."

New impetus has been given to the search for drugs having a selective effect on the different types of ocular nerves or muscles with an aim toward reducing the angle of deviation of the eyes. This approach may ultimately reduce the need for surgery in strabismus. Surgery long has been the main therapeutic approach to the cosmetic aspects of this problem; but because the cause of the deviation remains unknown, and because our techniques are based on empirically derived methods, surgical undercorrections and overcorrections are common even with the most experienced surgeons. Surgical research involves long term studies conducted on large series of patients treated by different techniques. Since standardized methods of measurement have to be utilized in such investigations, efforts must be made to encourage international societies to establish common evaluation and measurement techniques for diagnosis and therapy.

Ocular deviations involve not only children in the preschool years, but may also come on suddenly in the later years, often as a result of diabetes or neurological disease. When occurring in the older patient, there is usually paralysis of one or more of the muscles controlling the movements of the eyes. The paralysis may be due to disease or disturbance anywhere in the neural chain from the muscle back to the brain, and results in a most disturbing form of double vision for the patient. In a comparable situation, the young child partially suppresses vision in the turned eye, and develops amblyopia.

Two Harvard University scholars, working with newborn cats and monkeys, were able to create lesions outwardly similar to those resulting in some forms of strabismus and amblyopia. They then were able to observe selective changes which occurred in the animal's brain tissue and alterations in nerve impulses recorded at different points along the neural pathways to the brain. This work represents a major breakthrough. Their working model must be studied in depth, and other means of testing and evaluating these difficult cases defined. Likewise, the complex visual perceptual adjustments made by these patients must be explored in detail.

In addition, models treating the eye-brain-muscular system as a feedback control mechanism should be investigated further.

In this brief treatment we have not considered other difficult problems encountered in this phase of our work. As yet, we have little to offer most patients with nystagmus, an involuntary oscillation of the eyes which disrupts vision and creates major social problems for the patient. We also have to develop experimental models suitable for the study of visual perceptual anomalies such as dyslexia (in popular terms, "why Johnny can't read"). Adequately trained scientific manpower and an all-out, broadly based interdisciplinary effort are needed in this broad and difficult field.

NEURO-OPHTHALMOLOGY

Neuro-ophthalmology bridges the gap between neurology and ophthalmology. Since the eye is involved in practically all systemic neurologic disease and lends itself to thorough examination, the neuro-ophthalmologist often has the opportunity to diagnose a disorder elsewhere in the body at the earliest possible stage through a complete neurological eye examination. Many of the diseases he sees occur in infancy and childhood. Several genetically transmitted and degenerative diseases remain enigmas, and adequate treatments for these disorders must be defined. For example, important advances have been made in the handling of galactosemia, a metabolic disorder. Once the basic defect was pinpointed, simple dietary modification allowed prevention of ocular damage and mental retardation in many newborn babies.

The neuro-ophthalmologist plays an important role in the diagnosis of lesions occurring along the visual pathways. In addition, he is concerned with the diagnosis and cause of nystagmus and paralytic forms of strabismus.

Knowledge of the brain is only in its infancy. Understanding of its interconnections, chemistry, and structure may ultimately unveil the causes and mechanisms of diseases such as optic neuritis and multiple sclerosis, which result in visual symptoms and visual loss, as well as other bodily breakdowns.

The subspecialty neuro-ophthalmology requires extra years of training and is the least remunerative form of ophthalmic practice, hence, recruiting in this field has been a major problem. It is an exacting subspecialty requiring considerable time for the examination of the patient. Interdisciplinary cooperation and access to elaborate and costly equipment are necessary.

Basic research in this field will come from the neurobiologist, the neuroanatomist, the neuropathologist, the sensory communication scientist, and the bioengineer. The neuro-ophthalmologist's role will be to apply their findings at a clinical level.

CORNEA

The cornea is the highly transparent front outer coat of the eye. Opacification and surface irregularities impair or destroy its optical properties, thus causing visual loss or blindness, even when the light sensitive retina behind it is capable of normal function. Corneal diseases cause approximately 5 percent of the blindness in the United States. In other areas of the world, this percentage is far higher (see ch. 3).

Although many corneal diseases are congenital, degenerative, or due to nutritional deficiences, one of the most common causes of opacification is the scarring that follows injuries. Infections, lacerations, heat burns, and chemical burns all can cause opacification. Infections can be superimposed on injuries, or on nutritional or metabolic deficiencies, and lead to ulceration and subsequent scar formation. A small scar on the face following a cut might result in nothing more than a slight blemish. However, the same blemish on the cornea can scatter light or block light from reaching the retina. We need a better understanding of those factors providing and maintaining corneal transparency, and of those mechanisms controlling corneal wound healing and scar formation.

Probably more research effort has been expended on studies of corneal transplants than on any other

Figure 4.—A perimeter is used for detailed examination of the eyes to determine the outer limits of the field of vision and to detect areas of defective vision within the visual field.

aspect of corneal research. In the past few years, there have been great strides made toward the perfection of corneal transplant surgery. Some of these include the use of microsurgical techniques and the application of plastic materials as transplants. Although the number of successful corneal transplants is increasing because of improved techniques, there are still many unsatisfactory surgical results. Improvements are needed in methods of selecting and preserving donor material.

In the field of infectious diseases, herpes simplex, the simple cold-sore virus, has been responsible for corneal scarring with subsequent visual loss in thousands of individuals. One of the most exciting breakthroughs in therapeutics has been the recent discovery that this corneal disease can be attacked by the drug, IDU. This is one of the few drugs demonstrated effective against a virus disease. This discovery has opened up new approaches into the general study of antiviral agents. Many drugs which have been sitting on the shelf are now undergoing reevaluation in order to learn their effects on viruses.

The highly significant investigations of the corneal surgeons should be continued. Additionally, the physical and chemical nature of the cornea has to be explored in depth. Its unique metabolic properties, transparency, and reactions to infections and injuries must be understood in order to further the development of adequate treatments for corneal diseases. Similarly, in order to protect this tissue and the eye, it is essential that we advance our understanding of all external eye diseases.

TRACHOMA

Trachoma has been described as the greatest single cause of progressive loss of sight in the world.

Current World Health Organization (United Nations) estimates indicate that between 400 and 500 million people suffer from this disease. Although the viral cause of the disease has been known for many years, it was not until 1957 that scientists in Communist China for the first time isolated and cultured the virus in the laboratory. This accomplishment has stimulated efforts in laboratories all over the world.

The disease causes damage by the formation of scar tissue either on the cornea and/or the lids. It is usually a prolonged progressive disease which spreads within families or institutions, especially where hygiene is poor and fresh running water for cleansing is inadequate. In our country, we have eliminated this disease except among the American Indian population on the reservations in the desert Southwest.

It has been found that sulfonamides and some antibiotics provide effective treatment, yet reinfection is common when the living conditions are unchanged. Thus treatment of children in school is not sufficient when parents and grandparents at home remain untreated.

We must seek to break the reinfection cycle among these depressed and water-starved populations. In general, marked improvement in economic conditions and the general level of health education seem to be necessary.

Trachoma research has been progressing along many new lines. The new technique of immunofluorescence represents a major diagnostic breakthrough, allow detection of very early cases of the disease and indicating when a satisfactory cure has been obtained. We are seeking blood and skin tests diagnostic of trachoma, but so far none have proven practical. Drugs more effective than sulfonamides are being sought since the sulfas require prolonged therapy and are difficult to maintain in primitive populations. Further, these drugs suppress the trachoma virus rather than kill it.

Five institutions located in different parts of the world are engaged actively in human vaccine research. Seeking a vaccine against trachoma is fraught with many theoretical difficulties, but the worldwide importance of a possibly effective vaccine demands that research in this area be pursued. Even if only a partially effective vaccine were developed that could prevent reinfection, the whole picture of trachoma in our Southwestern Indians would be modified and an expensive and difficult family treatment program could be avoided.

In this area, the American ophthalmic research community can make a substantial contribution toward international well-being.

GLAUCOMA

The term "glaucoma" refers to a group of ocular disorders whose common denominator is an increase of pressure in the eye. Pressure elevations, if not reduced, can lead to damage of the optic nerve fibers and subsequent loss of vision. The process may end in total, irreversible blindness. Present figures indicate that glaucoma is responsible for 13.5 percent of the legally blind in the United States.

The normal pressure within the eye is maintained by a fluid (aqueous humor) which constantly circulates between the area of production (ciliary body) and the area of exit (trabecular meshwork outflow channels). In order for the eye to maintain a constant pressure, there must be a constant balance between the rate of production of the aqueous and the ease with which it leaves the eye. If this balance is altered, then the pressure in the eye must change. For example, if there is an obstruction to outflow while the rate of aqueous production remains the same, then the pressure within the eye rises. Similarly, if the rate of production is decreased while the ease of outflow remains the same, the pressure will fall.

The intraocular pressure of an individual can easily be measured by the use of various special instruments called tonometers. Other techniques, such as tonography and the suction cup method, provide us with valuable information concerning the rate of production of the aqueous humor and the ease of outflow through the trabecular meshwork.

Several populations have been surveyed in order to determine "normal" intraocular pressure. The problem is that not all eyes are damaged by the same elevated pressure levels. For example, one person may develop damage if his intraocular pressure is 25 mm Hg, whereas another individual with the same pressure may remain perfectly normal. More precise methods are needed to determine the susceptibility of an individual eye to damage. Similarly, long term follow-up studies (20–30 years) of survey populations are needed to determine whether those individuals with "high normal" pressure belong to a group that later develops glaucoma.

Many other problems remain. How the aqueous is actually produced is still a mystery. If we can learn the mechanisms of aqueous production, we will no doubt be able to advance glaucoma therapy greatly.

As a result of increased pressure in the eye, the optic nerve fibers degenerate. This degeneration either results from the effect of elevated pressure on the nerve, or from the pressure effect on the blood vessels supplying its nutrition. The time relationship between an increase in pressure and the appearance of optic nerve damage must be better defined.

Improved methods are needed for evaluating

Figure 5.—The only accurate method of determining the intraocular pressure of an eye is by use of a reliable tonometer. Here an applanation tonometer is used for this purpose.

clinically the amount of damage done to the optic nerve. Viewing the optic nerve directly with an ophthalmoscope enables the clinician to grade the tissue on the basis of appearance. Since glaucoma affects vision, the extent of optic nerve damage may be evaluated by visual field studies. Even finer diagnostic procedures must be developed if we are to detect the earliest signs of the disease.

Prevention of visual loss in glaucoma is accomplished by lowering the intraocular pressure. Various drugs can increase outflow, or reduce the rate of production of the aqueous. If medication is not successful, surgery is required. The surgical procedures are aimed at creating a new outflow channel allowing the aqueous to leave the eye.

One of the goals of preventive medicine is to be able to predict those individuals who most probably will develop a particular disease. This enables the physician to watch these patients more closely and to detect the very first sign of that disease. He then is able to treat at an early stage before serious damage occurs.

Because of the knowledge recently gained about the genetic and hereditary patterns of this disease, it is now believed that we will be able to predict which individuals are predisposed to develop glaucoma. With early treatment, there is no doubt that the number of people blinded from glaucoma will be greatly diminished.

These advances were made possible through studies such as the Collaborative Glaucoma Study and the recently devised steroid provocative test. It was shown that only part of the population developed glaucomatous levels of pressure and characteristic visual field changes when given locally administered steroid drugs. It has since been discovered that there is a relationship between this group of individuals and those most prone to develop glaucoma. All aspects of this finding are being investigated.

Glaucoma strikes over 2 percent of the population over the age of 40 in this country, many at the peak of their earning capacity. The incidence increases with advancing age.

CATARACTS

A cataract is any opacification or clouding of the lens of the eye. It may vary from a few small discrete spots to an area involving so much of the lens that effective blindness results.

Anything that can cause a physical or chemical alteration in the lens proteins may be responsible for the production of a cataract. This is why cataracts are often an associated finding in ocular anomalies such as uveitis, intraocular tumors, and other diseases which disturb the normal metabolism of the eye. They can occur as a congenital defect, or be the result of changes associated with the aging process. Cataracts which appear as a birth defect may be related to a systemic disease; for example, if the mother has German measles early in her pregnancy, cataracts often occur in the newborn. Physical injury, certain drugs, and many forms of radiation can produce cataracts.

Most laboratory research on the lens of the eye attempts to define the chemical and physical changes associated with the development of cataracts in the eyes of experimental animals. Cataracts have been produced in animals by various means, such as elevation of sugar levels in the blood, X-ray irradiation, ionizing radiations, diets deficient in specific components, elevation of certain hormones, and administration of certain specific drugs.

Many interesting facts come to light in the study of the lens. For example, dogs commonly develop senile-type cataracts, whereas cats do not. Perhaps more important, no case of cancer of the human lens has been reported.

The most common type of cataract is the senile cataract, so called because it occurs most often in the eyes of individuals past middle age. Senile cataract is a leading cause of blindness (15.6 percent) in the United States, and over 60,000 individuals are blind from this condition. Incidence rises with increasing age.

At present, surgical removal of the cataractous lens is the only effective therapy for cataracts once they have formed. Procedures for surgical extraction of cataracts have not changed markedly in recent years, although many modifications providing increased safety and surgical effectiveness have been developed. Improved suture techniques, advances in instrumentation, and the introduction of microsurgical techniques have been the products of clinical research. The application of the enzyme alpha-chymotrypsin makes it easier to free the cataractous lens from its suspensory attachments (zonules). Cryogenic (freezing) procedures recently have been applied to ocular surgery. But surgical complications still occur, and they require continued study and the development of further improvement in techniques.

Patients who have had one or both cataracts removed often experience visual problems. Increased image size, reduced field of view, decreased ability to fuse the two retinal images, impaired estimation of distance, lens aberrations, and limited depth of focus are often disturbing to the individual. We need improved optical aids and contact lenses for these individuals.

We seek to determine the causes of cataracts and to define adequate preventive measures. The fine structure, the metabolism, and those factors which

contribute to the maintenance of lens transparency should be investigated in far greater detail. In this way we may hope to determine not only why diabetics and others with known abnormalities develop cataracts, but also why elderly people in apparent good health lose vision progressively from senile cataracts. Variations in geographical prevalence would also be of great interest in understanding the natural history of the disease.

UVEITIS

Uveitis, or inflammation of the uveal tract, presents a frustrating problem to both the researcher and the clinical ophthalmologist. This is a disease which often strikes young adults in their prime productive years.

In order to understand uveitis, it is necessary to define a few terms. An inflammation is the reaction of tissues to injury or infection. This can be acute (immediate) or chronic (long standing and/or recurrent). An antigen is any substance (usually a protein) which enters the body and is considered foreign by the body's defense mechanisms. The body reacts toward these antigens and renders them ineffective. This is known as an antigen-antibody reaction. For example, when specific antibodies react with the polio virus, they prevent poliomyelitis from occurring in the individual. However, the antigen-antibody reaction sometimes can be so violent that the reaction itself may be very harmful. Immunology is the science devoted to the study of antigen-antibody reactions.

The uveal tract is the layer which lies between the light sensitive retina and the white outer coat of the eye. The front portion of the uveal tract is made up of the iris and ciliary body, while the back portion comprises the choroid. The uveal tract is usually quite pigmented and contains many blood vessels. Uveitis refers to an inflammation of this layer.

Uveitis may be a primary disease, i.e., arising in the uvea itself, such as when the uveal tract is infected with syphilis or tuberculosis. Uveitis may also occur as a reaction to disease in a neighboring structure. An example of this would be the uveitis which can occur following rupture of the lens with leakage of lens material within the eye. Another example would be the uveitis that occurs when the neighboring retina is infected by the protozoa, Toxoplasma Gondii.

Unfortunately, there are many more instances of uveitis in which the cause is completely obscure. Many of these are believed to be due to some type of nonspecific antigen-antibody reaction as described above. One of the diseases which is believed to fall into this category is sympathetic uveitis. In rare instances, following an injury to an eye, the other, uninjured (sympathetic) eye may develop a severe uveitis. It is believed that the second eye has developed antibodies to its own pigment, causing a severe reaction.

As might be expected when so little is known about the cause of a condition, treatment is usually nonspecific. In most cases steroid drugs appear to suppress the uveal inflammation at least partially. However, such therapy usually fails to yield a real cure, and the eye frequently undergoes progressive degeneration unless the condition subsides by itself.

An important factor which makes the study of uveal inflammation extremely difficult is the unavailability of ocular tissues for laboratory study during the early stages of the inflammatory process. Generally, the eyes are not removed until the disease has run its course, and they have had to be taken out because they are blind and painful. Thus, only old, "burned out" lesions providing a nonspecific microscopic picture are available for analysis.

Attempts have been made to produce similar lesions in experimental animals. Fungi, viruses, and bacteria have been inoculated into their eyes and the reaction pattern observed. Another experimental method has been to produce antigen-antibody reactions in these animals. These studies have yielded some beneficial results and must be continued. However, it is obvious that entirely new approaches are required. Epidemiological studies would be of particular value. Special programs and clinics for the study of uveitis are needed. These clinics can provide the proper facilities and atmosphere where the clinician can team up with the basic scientist in the study of these important problems.

RETINA AND CHOROID

The retina is a unique and highly complex tissue which originates embryologically as part of the brain. There are a variety of diseases which can result in loss of the ability of the retina to convert light into nervous impulses, that is, loss of vision. Visual loss may occur in the central retinal area, the macula, which is responsible for reading fine print, or in the peripheral part of the retina which provides "side" vision. Some of these disorders may be birth defects, others may be inherited. A number are associated with the aging process. These diseases may be limited to the eye, such as in cases of retinal detachment, or may be part of generalized disorders. Diabetes and arteriosclerosis are two examples of the latter category.

Unfortunately, with increased longevity, large numbers of older persons are developing serious retinal complications. Among the most prevalent are senile and presenile macular degeneration and diabetic retinopathy. In most instances, we have no

adequate treatment for the ocular complications of these diseases. Collectively, retinal diseases have become the leading cause of blindness among our population. They account for approximately 40 percent of the reported blind.

Degeneration of the very sensitive macular area may occur as a localized effect of poor nutrition resulting from arteriosclerosis, popularly known as "hardening of the arteries." At least 20 percent of the blind suffer from senile macular degeneration. The incapacitating loss of central reading vision and fine visual resolution which occurs in these patients is a severe handicap in carrying out even the most routine tasks.

In medicine's long and persistent fight against diabetes, remarkable progress has been achieved. With proper pharmacological control, life can be prolonged for decades. But longstanding diabetes takes its toll in blinding diabetic retinopathy. Today, half of the longstanding diabetics develop this complication, often during their most productive years. Obviously, we cannot overlook this rapidly increasing threat to the vision of so many of our citizens.

A large variety of diseases of the retina and choroid involve man alone, and there is no suitable counterpart among laboratory animals. We must study the pathology, biochemistry, and neurochemistry of the tissues of individuals affected with these diseases. Surprisingly, in many such conditions, there has not been even a single study of the underlying tissue changes. Two other factors severely limit the study of the retina. The diseased tissue cannot be biopsied as can tissue elsewhere in the body; and the retina deteriorates very rapidly after death, making post mortem examination somewhat less than adequate. Somehow we must get around these restrictions.

By means of injection techniques, special stains, and new biochemical procedures, information concerning the working of the retina in the normal and abnormal state is accumulating. Studies of the blood circulation of the retina and choroid are actively being pursued in an effort to understand the effects that changes in circulation will produce, and how these changes simulate known disease states. We need additional investigations of the effects of radiation, injury, drugs, and the effect of generalized aging on retinal tissue. As with so many of the other diseases mentioned, the study of the basic biological processes of the retina is very important. Only through knowledge gained from these studies can we learn how to prevent and treat retinal disorders.

Genetics plays a significant role in retinal disease since it has been found that many of these conditions are inherited. Better tests are needed to discover disease carriers so that proper family counseling may be performed.

Continuous improvements are being made in psychophysical and electrophysiological testing methods employed in evaluating many aspects of retinal function. However, such testing is currently being conducted at a relatively small number of institutions. A comprehensive approach to retinal and choroidal diseases is necessary, but most laboratories and clinics excel in only one area. Retinal diagnostic and research centers must be created or strengthened.

On the bright side of the picture, retinal detachment surgery is saving many eyes once considered lost. Light coagulation, laser coagulation, vitreous and silicone transplants, and scleral buckling procedures are some new techniques available in this field. New diagnostic procedures allow us to detect and define several retinal diseases at earlier stages.

SYSTEMIC DISEASES

By virtue of the optical properties of the eye, we are able to view the retina and optic nerve head directly. The blood vessels nourishing the retina are the only ones which the physician can observe in an undisturbed state. Because of this, the eye has often been called the window to the body, since changes observed in the retinal blood vessels and the retina are often a reflection of changes occurring in the rest of the body. Thus many generalized systemic diseases are best followed clinically and investigated scientifically by ophthalmic methods.

There are a variety of diseases of the body which produce ocular changes that are threatening or destructive to vision. As pointed out above, one of the main ones is hardening of the arteries, which often results in retinal macular degeneration and severe visual loss. In most of these diseases, the underlying cause is unknown. Inherited defects may account for some of them. Specific tissue allergies probably account for others. In the majority of these, more information is required. The eye is particularly vulnerable because of its varied metabolic patterns. Within the small unit of the eye are concentrated all three types of embryological tissue. Thus a disease usually occurring in one of these types of tissue will often affect similar tissue in the eye. For example, skin diseases often are accompanied by cataracts, because the lens of the eye has the same embryological origin as skin.

The eye is also vulnerable to nutritional disorders. Certain portions of the eye are fed directly by the bloodstream, yet other parts, such as the cornea and the lens of the eye, do not have blood vessels. As noted above, the latter are fed by exposure to the fluids which circulate through the eye. Disturbances in the composition of general body fluids will often be accompanied by changes in the cornea or lens because of alterations in the composition of their nutrient fluid.

Whether in the eye or elsewhere, the study of disease processes is often divided into four stages. Stage I represents the genetic and environmental factors that make an individual susceptible to a given disease. This is referred to as the predisease state. Newer therapies have increased the survival rate in diseases of genetic origin, allowing the affected individual to reach reproductive ages and increasing the prevalence of disease producing genes. The ophthalmologist must learn to recognize the subtle signs present in carriers of abnormal genes, and provide necessary eugenic counseling. In many recessive diseases, where the carrier exhibits no clinical signs, only the use of elaborate laboratory tests will reveal the abnormality. Animal inbreeding experiments may help us to ascertain the genetic influence in certain diseases.

Stage II represents the preclinical phase of the disease, the stage when the disease exists, but is not yet manifested by symptoms. Clearly, this is the stage which is most difficult to recognize, but during which treatment would result in most cures and least damage. Biochemical, electrophysiological, and pharmacological approaches often help to reveal this state. Extensive controlled studies are needed to determine what percentage of patients discovered in the preclinical phase of a disease will go on to develop the overt clinical disease. Only when these figures are known can a meaningful evaluation of the benefits of early therapy emerge.

Overt clinical disease represents stage III. Well-described clinical and laboratory observations of any particular disease and comparisons of various disorders have always been important. Such data suggest the questions and help formulate the theories upon which future investigations are based. However, description of clinical entities can go only so far. Extensive laboratory research and controlled clinical and animal experiments must go the rest of the way. This is especially true of uveitis, which is often associated with specific disturbances in other parts of the body. This relatively common disease tends to recur and subside, ultimately destroying the usefulness of the retina, or leaving the eye functionless from cataract or destroyed by intractable glaucoma.

Stage IV refers to the postdisease state or the "burnt out" phase of the disorder. This is the stage requiring maximal effort in the field of surgical research. New techniques are needed which will insure greater success and fewer complications. Furthermore, greater efforts must be expended in utilizing diminished visual capabilities through more efficient optical aids and rehabilitation programs.

DIABETIC RETINOPATHY

Remarkable progress has been made in understanding diabetes in the last 50 years. Therapeutic advances have allowed us to prolong life for 20 to 30 years. But with these advances has come a shift in the kind of complications with which we must deal. Whereas in previous decades we were faced with the acute problems of uncontrolled infections and gangrene, of metabolic imbalances and coma, we are now faced with the chronic problems of vascular disease and visual loss. Cataracts, involvement of intraocular blood vessels, and retinal changes present serious threats to vision. Cataracts can often be corrected by surgery, but the blood vessel changes and retinal involvement referred to as diabetic retinopathy can affect vision irreparably.

The incidence of retinopathy increases with the duration of diabetes. Prior to the introduction of insulin therapy, retinopathy seemed to develop only in diabetics over 40. The juvenile diabetics failed to develop retinopathy in that era because they did not live long enough. In 1934 the incidence of retinopathy among diabetics was reported as 17.7 percent; in 1945 as 29.6 percent; in 1955 as 47 percent. The growing importance of this complication (see fig. 3 in ch. 3) is emphasized by recent reports from Massachusetts and New York, where 18 percent and 19 percent respectively of newly reported cases of legally defined blindness were due to diabetes. The reasons for this complication remain unknown, and the changes which accompany it cannot be prevented by present methods.

It is generally accepted that the tendency to diabetes mellitus is inherited, although the mechanism has not been defined. It is not known whether the specific features seen in some diabetics, including the deficiency of insulin and the tendency toward complications, are inherited separately, or whether they are different manifestations of a single inherited defect. Normal people with a family history of diabetes exhibit a variety of changes that are not found in individuals without a similar background. These people have been called prediabetics, and rigidly controlled studies are needed to see if therapy can prevent them from developing diabetes.

Studies of the microscopic structure of the blood vessels in the retinas of diabetics and normal people have revealed specific differences. We are now investigating the biochemical nature of these changes, since diabetes is a metabolic disease with numerous biochemical imbalances. In particular, the relationship of insulin to these ocular complications is receiving much attention.

Retinopathy occurring in laboratory animals is not exactly analogous to that seen in human diabetics—a serious deficiency when we attempt to

Figure 6.—Inspection of the interior of the eye is accomplished through an ophthalmoscope. Here the examiner uses his right eye for observation of the right eye of the patient, keeping his index finger on the lens dial.

evaluate different methods of treatment. Clinical studies on human subjects often are made difficult by the differing rates or progression of the disease and its complications.

Therapy of ocular complications is complex and controversial. Surgical approaches, such as operations on the pituitary gland and coagulation of bleeding blood vessels in the eye, are difficult to evaluate. Results have been inconsistent and surgical complications do occur. It is apparent that further well-controlled surgical studies and new approaches are needed.

BIRTH DEFECTS

Through the diligent efforts of researchers and clinicians, great strides have been made in the treatment of eye disorders of the newborn. For example, gonorrheal infection of the eyes of infants has been virtually eliminated. Likewise, our conquest of retrolental fibroplasia in the mid-1950's has already saved the sight of 10,000 to 20,000 children who otherwise would have been blinded by the disease.

Abnormal growth and development of the eye before birth (congenital malformations) and/or during the first few years after birth (developmental disorders) often result in severe visual disability in both eyes. Some of the responsible factors are heredity, maternal infection during pregnancy, and untoward reactions to drugs which are administered to the pregnant mother (for example, Thalidomide).

Laboratory studies recently revealed the presence of the German measles virus within the cataractous lenses of newborn infants whose mothers had the disease early in pregnancy. This important finding helps define the action of this virus in blinding babies before birth. A recently developed vaccine offers hope for the prevention of this disease and its dread complications in the newborn.

Intensive studies of the so-called inborn errors of metabolism are needed. If the abnormality can be identified early, proper treatment or dietary changes may prevent damage. For example, as mentioned earlier, an alteration of the diet in infancy can prevent the development of cataracts, mental retardation, and eventual death from galactosemia.

In the fields of genetics and cytogenetics (the study of genetic patterns in single cells), rapid advances are being recorded. New laboratory techniques have enabled investigators to discover such abnormalities as extra chromosomes, missing chromosomes, and

defective chromosomes. Many of these findings subsequently have been correlated with specific disorders.

RETROLENTAL FIBROPLASIA

This blinding disease was first described in 1942. Its incidence among premature infants increased rapidly thereafter. Through cooperative studies involving several medical institutions, it was discovered that this disorder was related to the exposure of premature infants to high concentrations of oxygen.

The blood vessels in the premature infant are not fully developed. These premature infants, however, were placed in incubators in which high oxygen concentrations were maintained, because it was felt that this was necessary for the survival of the child. The high concentration of oxygen caused the developing retinal blood vessels to stop growing. The incubator oxygen levels were gradually reduced as the infant grew older, and the retinal blood vessels again started to grow. Only this time, there was an exaggerated overgrowth of these vessels in a disorganized fashion. This led to hemorrhages within the eye with subsequent scarring and blindness.

The discovery of the cause of retrolental fibroplasia represents a truly significant medical achievement. However, a number of questions still remain unanswered. Why do certain full-term infants who are not subject to high oxygen concentrations still develop retrolental fibroplasia, and why don't some premature infants who have been maintained under high concentrations of oxygen develop this disease? How do other environmental factors such as light and temperature influence the development of the eye in the newborn?

TUMORS OF THE EYE

Tumors in and around the eye may lead to serious visual loss, but more importantly, they may create life endangering situations. Because we often cannot obtain biopsies, accurate diagnosis of ocular tumors is not always possible. Many benign tumors closely resemble malignant tumors. About 20 percent of the eyes that are removed because of suspected cancer turn out to have only benign lesions. On the other hand, failure to remove a malignant tumor may result in the patient's death.

Retinoblastoma is a malignant tumor of the retina found in children. It occurs in 1 out of 25,000 births. In the past, it was almost invariably lethal. Today, because of earlier and more exact diagnosis, it is possible to save the child's life in over 90 percent of cases. However, there are still many difficult problems in arriving at a correct diagnosis, again because of the many benign conditions which resemble retinoblastoma. Since most of these tumors are treated by removal of the eye, there continues to be a need for the perfection of other methods of treatment which will permit preservation of the eye and its function. This includes continued investigation of the efficacy of X-ray therapy and anticancer drugs. Physicians need to be better informed about the genetic aspects of this disease so as to be better able to properly advise parents and survivors about the chances of the tumor appearing in other members of the family.

The most common ocular tumor found in adults is malignant melanoma. The frequency of this tumor ranges from 1 to 7 per 10,000 Caucasians. Therefore, it is not a rare disease, except, of course, in Asia, Africa, and other places where the population is largely nonwhite. The tumor is located in the uveal tract and has the potential for producing the pigment, melanin. The cause of this cancer, as is the case in almost all cancers, is obscure.

This highly malignant tumor has the potential for rapid spread throughout the body. Often, by the time the patient experiences some visual defect, the tumor has already silently spread to the liver or the lungs. Hence, we urgently require improved early diagnostic techniques. Some new methods offer promise; these involve the injection of chemicals which localize specifically in the tumor and can be picked up by X-ray or geiger counter. Continued study is also needed to uncover some of the riddles concerning the basic biology of these tumors. For example, why do some patients die within a year or two after the disease is discovered, while others live for 15 to 20 years after the tumor has been found?

As pointed out previously, the ophthalmic surgeon often cannot obtain the biopsy which is so important in confirming or rejecting his suspicions regarding a growth. Once the eye is opened to obtain a small piece of a choroidal tumor for biopsy, there is a loss of fluids and irreparable damage to ocular tissues with subsequent alterations in function. With the use of the recently developed cryosurgical (freezing) instruments, it is hoped that biopsy and excision of choroidal tumors may be possible.

Tumors of the eyelid and conjunctiva are fortunately seen early. However, it is still not clear whether these tumors are best treated by surgery or by X-ray. Tumors in the orbit (the bony cavity which houses the eye) are "hidden" lesions. Unlike those of the lids and the eye, they cannot be examined directly except by surgical exploration. New dye injection techniques coupled with X-ray observations offer promise. These tumors range from benign cysts to lethal malignant tumors, such as the

rhabdomyosarcoma, which most frequently occurs in young children.

There are very few highly trained investigators working in the field. Clinical and basic scientists are needed. The training and coordination of efforts needed in this field can best be accomplished by the creation of one or more specialized eye tumor centers.

OCULAR INJURIES, PROTECTIVE DEVICES, AND AUTOMOTIVE SAFETY

Injuries to the eye are more frequent and serious than most individuals realize. Since they usually affect only one eye, those involved generally do not appear on the rolls of the blind. When cases of monocular blindness are reviewed, it is discovered that children under 10 years old are injured three times more frequently than any other age group.

We need to develop thin, cosmetically acceptable protective lenses. The transparent organic plastics are good both as optical lenses and mechanical shields. Unfortunately, their present unsuitability lies in their relative "scratchability," which decreases the functional life of such a pair of glasses—particularly in the hands of children. Obviously, the surface hardness of these plastics must be increased while other attributes are retained.

Phototropic lenses are receiving great attention. These lenses automatically change their light absorbing power under different lighting conditions. Hence, they adjust to protect the eyes of the individual in changing environments. For example, they would become lighter when a driver enters a darkened tunnel, stay lighter while he is in the tunnel, and darken again when the individual emerges into sunlight. They also will be valuable in the prevention of temporary or permanent flash blindness. Such devices obviously will have many important applications.

When prevention has failed, we face the problem of the management of ocular injuries or trauma. There is a pressing clinical need for the development of simple, compact, easily maintained, and economically procured microsurgical equipment. Such equipment would allow more accurate repair of ocular wounds and reduce surgical trauma in the removal of foreign material. And we need to perfect techniques useful in the localization and removal of nonmagnetic foreign bodies which enter the eye.

The continual increase in the number and speed of automobiles on the roads, and the proportional rise in the incidence of serious driving accidents, necessitates a review of driver visual requirements. More frequent visual examinations, and more adequate testing methods are badly needed. There is really very little data available on the relationships between visual acuity, the extent of visual field, light and dark adaptation capability, visual reaction time, good and bad eye movement patterns, and the incidence of automotive accidents. The effects of light absorbing tints and distortion effects in windshields must be considered. Similarly, optimum size and angle of the windshield in relationship to the driver should be specified. The adequacy, number, and location of rear view mirrors and the requirements for car and road lighting need evaluation. In general, research is needed on the ways to optimize the design of the automobile, the highway, highway signs, and the various means for control of the visibility of the environment of the driver so that visual factors as a cause of highway accidents can be reduced and even eliminated.

OPHTHALMIC TOXICOLOGY AND PHARMACOLOGY

Ocular contact with toxic agents, either externally through exposure to substances in the environment or internally via the bloodstream, is of increasing importance. Modern industry has provided our households with all varieties of cleansers, detergents, polishes, insecticides, and aerosols. Aerosols are of special importance because they so readily come into direct contact with the eye. "Hair spray conjunctivitis" is now a clinically recognized form of disorder.

Chemical injury to the eye is an occupational or incidental hazard in an infinity of tasks. The worst injuries involve strong acid or alkali burns, which destroy much of the front of the eye. Often damage occurs so rapidly that little can be done when the patient is seen by the physician. Less severe exposures can also produce serious damage requiring difficult procedures. Clearly there is a need for expansion of research on the chemical and biological changes which occur in the cornea and adjacent tissues when they are subjected to the action of injurious chemicals. Fortunately, education and safety precautions are reducing the incidence of industrial cases.

Pharmacology has provided us with a constant stream of new drugs which, when taken orally, ultimately circulate through the eye. Most have been completely innocuous, but others have affected the eye and visual mechanisms. Cataracts, damage to the optic nerve resulting in partial or complete visual loss, erratic ocular movements, and occasional hemorrhages have been recorded. In many cases, the Food and Drug Administration (FDA) has prohibited the use of drugs causing serious ocular side effects. In other cases, the need for (or the effectiveness of) some drugs may be so great that the physician risks an ocular complication in the course of therapy. What is needed is continued vigorous pharmacological research to alter these drugs in such a

way as to preserve their useful powers and eliminate the harmful ones. In practically every instance, there is a lack of sufficient knowledge of the mode of action of the injurious substance. This lack of knowledge also inhibits the logical development of highly specific antidotes to counteract drug poisoning of the eye. In addition, systemically administered drugs should be more adequately pre-evaluated for ocular complications.

Few ophthalmic pharmacologists currently exist, and the reporting, collecting, and screening of adverse drug reactions is not adequate. Of equal importance, experimental work is needed to develop new and effective pharmaceuticals for the treatment of many eye disorders.

REHABILITATION OF THE BLIND AND PARTIALLY SIGHTED

There are few among us who would deny the very best of training, care, and auxiliary aids to the 400,000 legally blind, or to the far larger group of individuals who have experienced significant visual loss. Yet, we discover that there are comparatively few research programs being conducted under NINDB auspices on rehabilitation and teaching methods for these individuals. This is a consequence of the lack of trained research workers in this field, and the problems encountered in the definition of suitable research models.

Many ingenious devices are in development to assist the visually deprived patient read, get about, and otherwise enrich his limited world. However, the depleted resources of these individuals and their families (and the limited funds available to charitable agencies), and the presence of other infirmities, old age, and complex emotional problems often preclude the utilization of complex devices designed in their behalf. We need to teach the engineer the problems of the blind, and the social worker and the teacher the capabilities of modern science. We must continue to define suitable tasks for the visually impaired, and to conduct research into the ways and means of making their lives more meaningful.

What methods of education are best for the blind child and adult? How does auditory learning compare with braille reading? What teaching devices are being used, and how can they be improved? What are the behavioral problems of blind children, and what are the best ways to cope with them? How do we select the best types of individuals to teach blind children, and how shall we train them? How can we most effectively rekindle hope in the adult and, in particular, the aged? What is the general attitude of the public toward the blind individual? And can this be improved through educational campaigns?

Programs to help the partially sighted (as distinguished from the totally blind) represent an extremely important part of the rehabilitation program. We try to make the most of their residual visual functions. The use of special optical aids for individuals with subnormal vision has grown tremendously in recent years. Increased emphasis on the use of optical aids in the training of these patients, and the availability of the financial support needed to set up and maintain special clinics for the partially sighted have contributed to this trend. The Vocational Rehabilitation Administration has played an important role in these efforts.

We need to better inform clinicians concerning the problems and resources of the blind and visually impaired patient.

CONCLUSIONS

We have sought to present a concise statement of the present state of research on vision and its disorders. Important advances have been made, and opportunities for still greater progress are clearly present. Yet, in reading this chapter, one cannot fail to be impressed by the breadth and enormity of the task that still faces us, and its importance.

Chapter 3—CAUSES AND COSTS OF VISUAL IMPAIRMENT

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PREVALENCE OF VISUAL DEFECTS

An estimated 3.5 million Americans have some visual impairment. Nearly one million have a severe visual defect, and of these, more than 400,000 are legally blind (*1*).

These are disturbing statistics. Perhaps more disturbing is the fact that the number of those with visual defects is growing more rapidly than the population. In 1940, 175 out of every 100,000 people were blind. By 1962, the rate had increased to 214 per 100,000 (*2*). With population increasing rapidly during this period, the result was a near doubling of the number of the blind (see figs. 1 and 2).

The prevalence of less severe effects is harder to measure. Tens of millions of young Americans have visual problems. Nearly everyone requires eyeglasses at some time during his life. An estimated 1,335,000 persons 40 years of age and over have glaucoma (*3*). Many of these people do not know that they have the disease and may lose vision if untreated.

Reliable estimates of the prevalence of all visual defects and eye diseases are not available. Generally, the only statistics which can be obtained are for the number of people who are legally blind. Even these figures are approximate, for the definition of blindness varies from place to place, as do reporting procedures. There is a great need for better and more uniform collection and reporting of such data.

Blindness is usually defined as a defect sufficiently severe to prevent a person from performing work for which vision is needed. It is therefore a more general term than "total" blindness, which is the inability to distinguish light from darkness. In 1934, the American Medical Association proposed the following standard for determining blindness: "Vision in the better eye, with the best possible correction, of less than 20/200, or an equally disabling loss of the visual field" (*4*).

This definition was incorporated into the regulations of the Social Security Board in 1936. There was no requirement that it be adopted by the States, each of which established its own standards, or none at all. It continues to be the most widely used definition.

In 1962, a great step forward in gathering information about eye defects was made with the establishment of the Model Reporting Area for Blindness Statistics (MRA), sponsored by the NINDB, with the cooperation of other Federal agencies and voluntary organizations. The MRA is an association of States which maintain registers of blind persons, and which have joined together in a pioneering effort to collect uniform information. States participating in the MRA have all adopted a definition of blindness somewhat improved over that given above: "Visual acuity of 20/200 or less in the better eye with best correction, or visual acuity of better than 20/200 if the widest diameter of the field of vision subtends an angle no greater than 20°." The Subcommittee asks all States to adopt a common set of standards for gathering ocular morbidity statistics.

Despite these advances in the reporting of blindness statistics, no very firm figure as to the total num-

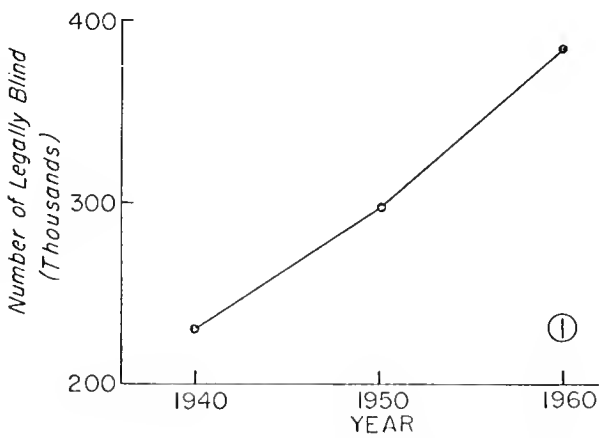

Figure 1.—The number of legally blind in the United States, 1940–60. Source, the National Society for the Prevention of Blindness.

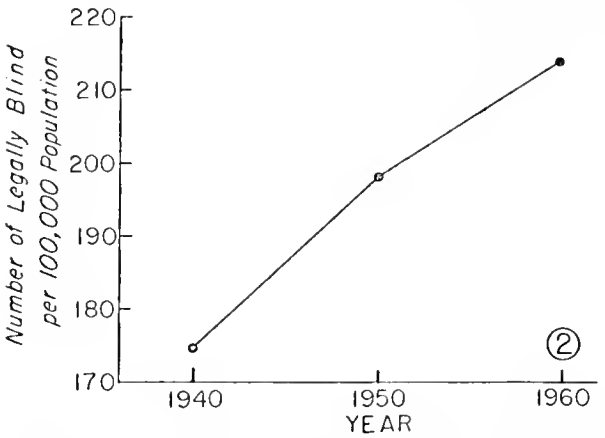

Figure 2.—The number of legally blind per 100,000 U.S. population, 1940–60. Source, the National Society for the Prevention of Blindness.

ber of blind in this country is yet available. It is possible to make fairly good estimates based on data from the MRA and from previous studies, but these remain estimates. They are probably low estimates. We know that most agencies reporting the number of blind miss many cases because people with severe visual defects are often reluctant to report themselves as blind.

A number of individuals may be able to conceal their defect. Some can distinguish shapes and colors, avoid obstacles, and recognize people by their voices. They may wish to conceal their disability simply from pride or for fear of losing privileges (such as a driver's license) or their job.

An undetermined number of blind persons never appear in statistical surveys simply because they are essentially out of reach of public and private organizations. A blind person who is not working and who is not receiving welfare payments from local or Federal agencies may never come to the attention of a data gathering group.

For these reasons, we assume that the estimates for the number of blind given in this chapter are probably low. They are, however, the best figures available. Estimates of the prevalence of eye defects which cause damage short of blindness are even more difficult to obtain. The most reliable source of morbidity statistics in this country is the National Health Survey (*1*) established by the Federal Government 10 years ago. Most of the estimates of the prevalence of diseases and defects given here are derived from NHS estimates.

The NHS derives its figures from several sources. They interview a broad sampling of the population, and perform direct physical examinations on a small number of individuals. They also collect statistics from voluntary organizations and other agencies which routinely gather data on the incidence and severity of diseases.

INCREASING INCIDENCE OF BLINDNESS

From figures 1 and 2 we can see that not only the number of the blind, but the proportion of the population which they represent, is increasing (*2*). This seems a puzzling circumstance in an age of rapidly improving medical care. The irony of the situation lies in the fact that it is most probably modern improvements in medical care which are the cause of the increasing rate of blindness in our population.

This unhappy situation stems from two causes. First, we know that many of the serious blinding diseases are diseases of middle and old age. Beyond the age of 40 or 50 an increasing proportion of the population suffers from retinal diseases, glaucoma, cataracts, and other major causes of blindness. As the older portion of our population increases, we can expect the incidence of these blinding diseases to go on increasing. Two thirds of the blind are past the age of 45 (see table 2). Second, to a certain extent the increase in the number and proportion of the blind can be attributed to specific successes in other

Table 1.—*Estimated new cases of blindness—1960 and 1962* [1]

Cause	Number		Percent
	1960	1962	
Infectious diseases	670	690	2.2
Syphilis	330	340	1.1
Other	340	350	1.1
Injuries	570	600	1.9
Poisonings	140	160	.5
Retrolental fibroplasia	50	60	.2
Other	90	100	.3
Tumors	530	530	1.7
General diseases	7,470	7,740	24.7
Diabetes	4,330	4,480	14.3
Vascular	2,700	2,790	8.9
Other	440	470	1.5
Prenatal influence	6,110	6,330	20.2
Glaucoma	4,380	4,550	14.5
Senile cataract	4,160	4,290	13.7
Myopia	990	1,030	3.3
Miscellaneous	2,200	2,290	7.3
Undetermined or unspecified	3,030	3,140	10.0
Total	30,250	31,350	100.0

[1] National Society for the Prevention of Blindness.

Table 2.—*Estimated distribution of total blind population by age—United States, 1962*

Age	Percent of total [1]	Number [2] legally blind
0 to 18	8.27	33,022
19 to 29	7.55	30,147
30 to 44	12.94	51,669
45 to 64	24.13	96,351
65 and over	45.61	182,121
Unknown	1.50	5,990
Total	100.00	399,300

[1] Based on Hurlin, 1962, p. 10.
[2] Estimated 1962 total from National Health Survey.

areas of medical research. As an example, insulin treatment has extended the life span of diabetics by decades. As a result, the incidence of diabetic retinopathy (and other ocular complications of long standing diabetes) has increased sharply as a cause of blindness in this country (fig. 3). As can be seen in table 1, blindness indirectly caused by diabetes currently accounts for about one-seventh of all new cases of blindness.

CAUSES OF BLINDNESS

In table 3 which is based upon statistics gathered by the Canadian National Institute of Blindness, we can see that there are about 75 different entries in the column "Causes of Blindness." These 75 categories are by no means exhaustive as some of the headings include many different diseases.

In table 4 we show a considerably simplified categorization of the causes of blindness in this country based on estimates prepared by the National Society for the Prevention of Blindness. The categories are quite arbitrary and the estimates, of course, are not precise figures. When comparing tables 3 and 4, we can see that the U.S. estimate comes fairly close to reproducing the more precise figures collected by the Canadian group with some differences.

In order to appraise differences between tabulations of this sort, one must know if those responsible for making these designations had an opportunity to examine the patient, and/or had access to the patient's records. Similarly, guidelines used in tallying the morbidity statistics may differ. A problem often is encountered if the patient is not categorized until "after the fact." A dense cataract may result as an aftermath of (or during) an infectious disease, an injury, a toxic drug, or a metabolic disorder, or it may occur as a manifestation of the aging process. Categorization is dependent upon information available, and the classification system employed.

One of the reasons that lists of the causes of blindness are so long is that the eyes are often severely affected by disturbances occurring elsewhere in the body. An infection which may produce no permanent damage at its original site may, as a side effect, produce irreversible loss of sight. Only slight damage to the eye may be disastrous: a damaged area in the macular region of the retina—the size of a pin head—may produce legal blindness.

In a vast number of cases we simply do not know the immediate cause of blindness. In fact, in the great majority of cases, we are ignorant of the ultimate cause or underlying mechanism producing loss in sight. Considering the extremely diverse nature of disorders which may lead to visual impairment or to blindness—ranging from keratoconus, which

Table 3.—*Causes of blindness in Canada*[1]

Causes	Number	Percent
Glaucoma	2,138	9
Cataract	1,751	7
Myopia	1,404	6
Macular Degeneration	716	3
Other, Specified	442	2
Infectious Diseases		12
Diphtheria	4	
Gonorrhea, excluding ophthalmia neonatorum	1	
Measles	102	
Meningococcal meningitis	115	
Ophthalmia neonatorum:		
Gonorrheal	32	
Other infection, specified	3	
Type of infection not specified	766	
Scarlet fever	27	
Septicemia		
Smallpox	22	
Syphilis	672	
Trachoma	144	
Tuberculosis	235	
Typhoid fever	16	
Rubella	1	
Onchocerciasis		
Toxoplasmosis	31	
Brucellosis		
Leprosy		
Other infectious disease, specified	353	
Infectious disease not specified	541	
Trauma		5
Chemical causing burn	89	
Radiation	16	
Other object or substance causing burn	8	
Firearm using explosive	122	
Airgun, slingshot, etc.		
Fireworks (any type)	6	
Other explosive	282	
Sharp or pointed object	136	
Blow or fall	268	
Foreign body in eye	120	
Other agent or source, specified	143	
Agent or source not specified	157	
Poisonings		2
Methyl alcohol	63	
Dinitrophenol		
Lead	7	
Quinine	1	
Excessive oxygen	332	
Other poison, specified	34	
Kind of poison not specified	4	
Neoplasms		1½
Retinoblastoma	52	
Melanosarcoma	6	
Neoplasm, other types specified	286	
Neoplasm, type not specified	11	
Diseases not elsewhere classified		16
Anemia and other blood disease	60	
Diabetes mellitus	1,238	
Nephritis and other kidney disease	62	
Vascular (including arteriosclerosis and cerebrovascular)	1,167	
Multiple sclerosis	167	
Disease of pregnancy	37	
Nutritional deficiency	84	
Other diseases not elsewhere classified, specified	999	
General disease not elsewhere classified or specified	17	
Prenatal influence (not elsewhere classified)		32
Genetic origin, established by family history	3,904	
Genetic origin, presumed	3,979	
Prenatal influence, cause not specified	16	
Evidence insufficient for diagnosis	786	5
No report on etiology	438	
Total	24,605	100

[1] Canadian National Institute for the Blind, 1965.

Table 4.—*Estimated percentage of legally blind persons, by cause and age group, United States, 1962* [1]

Cause	Total	Under 5	5 to 19	20 and over
Infectious diseases	5.2	3.8	3.9	5.4
Ophthalmia neonatorum (O.N.)	.3		.3	.3
Syphilis	2.1		.3	2.3
Other	2.8	3.8	3.2	2.8
Injuries	2.9	1.1	2.4	3.0
Poisonings	3.5	14.1	33.3	.4
Retrolental fibroplasia (RLF)	3.2	14.1	33.3	.1
Other	.3			.3
Neoplasms	1.4	5.0	3.5	1.2
General diseases	20.4	1.5	1.6	22.4
Diabetes	11.2			12.4
Vascular	7.6			8.4
Other	1.6	1.5	1.6	1.6
Prenatal influence	16.7	64.6	47.7	13.2
Glaucoma	13.5			15.0
Senile cataract	15.6			17.2
Myopia	4.3			4.8
Other specified	4.6	2.7	1.4	4.9
Undetermined and not specified	11.9	7.2	6.2	12.5
Total	100.0	100.0	100.0	100.0

[1] National Society for the Prevention of Blindness.

causes the cornea to become thin and distorted, to the perceptual anomalies of vision—the research progress which will be required for a full understanding of the causes of these disorders is truly enormous. It will clearly require a concerted effort from all the scientific and medical disciplines which bear on these diverse problems.

One of the first requirements will be, as was noted above, better statistics as to the relative prevalence of disabling eye disorders. Even for the task of planning the allocation of our research effort, we need more facts.

THE COST OF VISUAL IMPAIRMENT

There are three kinds of costs which can be attributed to disorders of vision. The first are direct costs in the form of aid to the blind and the costs of medical care and rehabilitation. Secondly, there are the far higher costs of lost productivity from afflicted individuals and thirdly, there are the intangible costs of suffering and deprivation.

None of these costs are easy to estimate. From a number of different sources we can get a rough indication of the magnitude of direct costs of visual impairment. Federal payments to the blind amount to more than $95 million annually (*5*). Based on figures available from New York and Massachusetts, we can estimate payments for direct aid to the blind from the States during 1964 at between $600 and $900 million (*5*). With increases in both the costs and the number of the blind (figs. 1 and 2), we can estimate that the annual bill simply for direct aid to the blind now approaches $1 billion. To this we must add the cost of care and rehabilitation and the cost for special education and medical care which are borne by the victim's families, or which come from sources other than State or Federal aid.

These are admittedly rough estimates. The loss in economic productivity which follows visual impairment is even more difficult to determine. The U.S. National Health Survey, using data collected between 1959 and 1961, estimated that 3.5 million Americans were visually impaired or blind. Of this number, many had a partial or total restriction upon their ability to engage in productive activity. The following data are taken from the USNHS report (*1*):

Number of people	*Category*
1. 87,534	Males and females, ages 14–65, who are unable to engage in the major activity of their group (work, housework, education) because of severe visual impairment or blindness.
2. 257,940	Males and females, ages 14–65, who have a lesser activity limitation because of severe visual impairment or blindness.

To translate these figures into economic loss, we assume that the average wage earner in this country currently earns $5,800 per year (*6*). We assume that people in category 1 earned no income, and that the partially disabled in category 2 earned 50 percent of their normal income, or $2,900 per year. Since the numbers of blind and partially sighted have been increasing rapidly in our population (figs. 1 and 2), and the data presented in the USNHS were gathered in about 1960, we feel justified in increasing the number of individuals in category 1 to 100,000, and those in category 2 to 290,000.

Number × *loss per year* = *total loss per year*

1. 100,000×$5,800 = $580,000,000
2. 290,000×$2,900 = $841,000,000

Combining the two figures we find an estimated deficit in earning capacity of $1.42 billion. Adding together the estimated cost of direct aid to the blind and the losses of economic productivity from the blind and the partially seeing, we find that the present cost to the Nation of visual disorders exceeds $2.4 billion yearly. It hardly needs to be repeated again that this is a rough approximation.

It is important to point out that jobs provided for the visually handicapped may not fully utilize the prior training of the individual. Most skilled and highly salaried tasks require keen vision. Our society imposes great visual demands on the machinist, the accountant, the engineer, the chemist, the administrator, and many others. Many of the partially sighted cannot sustain employment, nor compete successfully in such fields. Of course, there

are always outstanding individuals capable of rising above their afflictions, and there are a limited number of occupations where they may continue their activities.

We have already noted above that the special costs of rehabilitation, education, and care, which are often borne by the families of the blind and visually impaired, or by charitable institutions, do not appear in the $2.4 billion figure, nor do a number of other direct costs of blindness. The Library of Congress, for instance, is spending $2,675,000 this year for its "talking books" program. The Publishing House for the Blind receives approximately $1 million in direct Federal aid. The Veterans Administration has a very substantial yearly expenditure for the blind through its pensions, and rehabilitation and prosthetic appliance centers, in addition to purely medical care. Accurate estimates for total VA aid are not available, but as of September 1962, compensation and pension payments to veterans whose major liability was listed as blindness were about $17 million annually (*7*). In 1963, the Internal Revenue Service allowed the legally blind tax relief estimated between $8 and $11 million. Unfortunately we do not know how much income these individuals earned, nor what proportion of them were wage earners. The Vocational Rehabilitation Administration and other agencies maintain substantial programs for the visually handicapped.

As noted above, available estimates of the number of blind in this country are probably low. And too, we know that many of the blind are stricken during their peak years, since many of the major disabling eye diseases increase in frequency with increasing age. On the basis of statistics from North Carolina (*4*) we estimate that just less than half of all those presently blind fall between the ages of 19 and 65.

The age at which blindness appears is, of course, very important in these estimates. The wage-earner and head of household who becomes blind deprives his dependents of support and at least temporarily becomes a dependent himself. Yet it is also true that a disease which appears in early childhood or infancy is in a sense more damaging, because visual disorders do not generally shorten life expectancy, but tend to markedly reduce the productivity of the individual, and obligate society to provide lifelong assistance. From Bureau of the Census figures, we can estimate that a boy born in 1962 could expect lifetime earnings of about $240,000 (*8*). It has been estimated (*9*) that care for the blind person over a lifetime costs roughly $100,000 at present levels. Each blindness in infancy therefore may cost us, directly and indirectly, upwards of $340,000 over the person's lifetime. Effective educational programs and vocational rehabilitation in many cases can substantially reduce this figure.

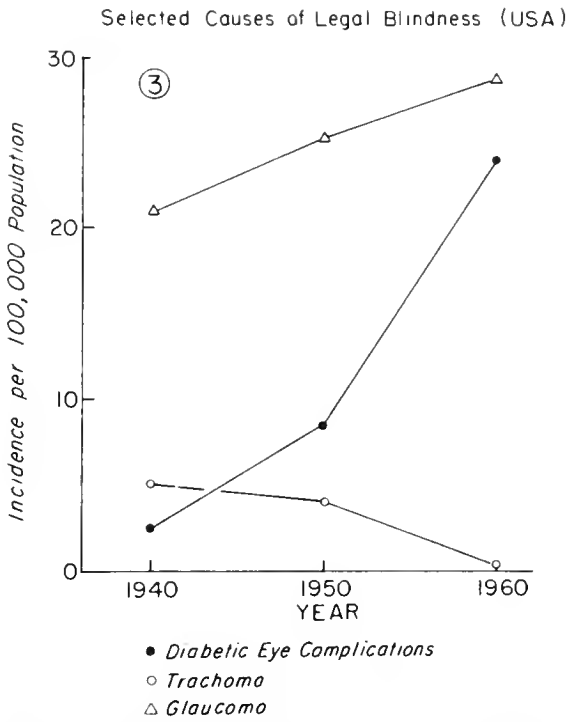

Figure 3.—Prevalence of legal blindness per 100,000 U.S. population caused by selected eye diseases, 1940–60. Source, the National Society for the Prevention of Blindness.

It is, of course, difficult to know which of many possible methods of estimating the cost of visual impairment to the nation to use, and it is simply impossible to set a price on the costs in suffering which visual disorders cause. All things considered, we believe that the estimate given above of the cost of blindness and visual disability to the Nation of $2.4 billion annually is a low estimate. In any case, we are certain that it gives an accurate idea of the magnitude of the cost of these disorders—which is unquestionably in the billions of dollars annually—in this country alone.

As a world problem, visual disorders are even more important than they are in the United States. More than 60 percent of the blind suffer from the disease trachoma, which affects one-seventh of mankind (*10, 11*). One finds numerous communities in Aden where the incidence of trachoma exceeds 90 percent, and in the State of Punjab in India 79 percent have the disease (*11*). Yet in figure 3 we see that we have virtually conquered the disease in this country. The only remaining pocket exists among the American Indians in the southwest.

No attempt has been made in this report to describe the enormous cost of visual diseases and disorders in other countries; nor have we attempted to define the enormous potential benefits to the world of the eye research program being conducted in this country.

SUMMARY

The current situation was well phrased by Undersecretary of Health, Education, and Welfare, Wilbur J. Cohen, in a passage from a speech defining the extent of the problem facing practitioners and investigators in vision and its disorders:

"Unfortunately, the incidence of blindness is increasing in this country. Between 1940 and 1960, the percentage of blind persons in this Nation increased much more rapidly than the population in general. In contrast to a general population increase of 36 percent, the blind population increased some 67 percent. In just 1 year alone, 1964, 31,800 people first became afflicted with blindness.

"Today, in the United States, there are about 400,000 blind persons and 3,500,000 persons with only partial vision. About 1 million people have a visual impairment severe enough to prevent them from reading a newspaper. Cataracts, glaucoma and diabetes account for about one-half of the blindness in this country—and the sad thing is that much of this blindness could be prevented through early detection and treatment.

"There are about 70 million persons over age 40 with a visual problem; it is estimated that this number may rise to 80 million by 1980. There are about 56 million children under age 15 with visual problems and it is estimated that this number may increase to 75 million by 1980. Thus, it is important that we mobilize all of our resources to cope with this growing incidence of visual defects.

"In the face of this rising tide, one of our great hopes is research. The job has really just begun" (*12*).

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status of research in vision

part II

Chapter 4—RESEARCH ON VISION PHYSIOLOGY, REFRACTIVE ERRORS, AND RELATED OCULAR ABNORMALITIES

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This report is an attempt to evaluate the current status of knowledge in the area of vision physiology and its abnormalities; to point out a few of the most important recent breakthroughs; and to outline recommendations for future progress in this area. In addition, an appendix outlines the sort of institutions currently carrying out research in this area and how their efforts are channeled. The appendix also includes a report on the incidence of spectacle wearers in Tecumseh, Mich.

In evaluating research in vision physiology, it is important to emphasize that much of it is fundamental for the advance of medical practice other than ophthalmology. Research on problems such as the nature of visual excitation, the coding of nerve impulse signals from the eye to the brain, and the perception of form, brightness, and color provides valuable insights for clinical neurology, neurosurgery, psychiatry, and psychology—insights which may have even more potential in these areas than in contributing to the ultimate conquest of blinding eye diseases.

CURRENT STATUS OF KNOWLEDGE

Introduction

In order to understand what is known about vision physiology and refractive anomalies, it is useful to draw an analogy between a television system, and the human visual system. The television system consists of a camera and a complex electronic device that converts an optical image of the real world into a series of signals, which are then coded and transmitted to a receiver. The receiver decodes this information and recreates the image. The television set (the receiver) is analogous to the visual centers of our brain; the television camera is analogous to our eyes. Of course, we have two eyes, so there the analogy breaks down. The two eyes allow a three-dimensional world greater fidelity in visual depth perception than is possible in a television system. The analogy breaks down also because the process of visual perception is itself accompanied by action—we move our eyes, we respond to changes in our visual world in thousands of ways. Since whatever is known about these aspects of visual physiology is to be covered in other reports, they need not trouble us here.

Optics of the Eye

Let us return to the single eye, the optical image-forming device of our vision-television analogy. The optical characteristics of the "normal" eye were reasonably well worked out by 19th century physiologists, and this work culminated in the award (in 1911) of the Nobel Prize in physiology and medicine to Prof. Allvar Gullstrand. A good summary of this work is available in English (*1*), and a recent review (*2*) adds some of the more important advances in this century. We know that most of the refraction in the eye occurs at the anterior corneal surface and that the lens acts as an automatic focusing device, so that objects at different distances are each, in turn, sharply focused. The lens is not homogeneous; it is made up of a large number of layers, one over the other, each of which has a slightly different index of refraction and, therefore, contributes to the focusing of the light rays.

The application of the principles of feedback control systems' engineering to the mechanism of accommodation (changes of lens form in changing focus from an object at one distance to one at an-

other) has promise for increasing our understanding of how this occurs. We know that a complex combination of stimulus factors (including defocus blur, perception of nearness and farness, and image size) help to signal whether an object is to be brought into focus by an increase or by a decrease in refractive power, but we do not understand the relative importance of these different factors and which (if any) are the crucial ones (*3*). We know only that the eye almost always goes in the correct direction, and that, if the stimulus suddenly changes, the accommodation mechanism will follow these changes as though the state of focus were being continuously monitored. The relevant nerve pathways to and from the brain are well worked out, but the connections within the brain are still only very poorly understood.

The changes within the eye are well described (*4*). Briefly, a contraction of the ciliary muscle relaxes tension in the fibers which support the lens; this, in turn, allows the elastic lens capsule to mold the lens so that its anterior surface in the center bulges forward, thus increasing the refractive power of the eye. The different regions of the lens are molded differently because of the differences in thickness of the capsule. The relaxation of the ciliary muscles (in looking from a near to a far object) increases the tension of the fibers supporting the lens and exerts tension on the capsule. The substance of the lens, now free of the molding forces placed on it by the capsule, reverts to a less convex form, and the refraction of the eye is decreased.

An increase in activity of the parasympathetic division of the autonomic nervous system increases the refractive power of the eye and an increase in the sympathetic division decreases this power. Of the two influences, the parasympathetic is about 10 times as great as the sympathetic. It is not known whether, in man, the two divisions of the autonomic nervous system act by operating on the same or on different ciliary muscle groups. Most evidence supports the idea that all muscle groups are innervated by both kinds of nerves.

In principle, accommodation can be achieved by means other than changes in curvature of the lens, and indeed other mechanisms have evolved in certain animals. The problems of accommodation are considered in further detail in the report on oculomotor systems.

In man, the lens continues to grow throughout life, the older lens fibers being overlaid by younger fibers. In the adult lens, the fibers gradually harden, and the accommodation power of the eye wanes. By the midforties, it has dwindled so much that we cannot read or do close work for a prolonged period through the spectacle lenses which we wear for viewing distant objects; we then need bifocals or trifocals or reading glasses. This condition is called presbyopia, and it affects all who live long enough. At the onset, while near objects can still be momentarily seen sharply at up to around 20 cm., the maximum amount the eye can increase its refractive power has fallen to about 1.5 diopters. We know that this decline in near vision begins very early in childhood. We do not know, however, whether, as one grows older, a greater and greater amount of change in length of the ciliary muscle is necessary for a unit change in refraction of the eye (*5*).

The aperture stop of the eye is the inner border of the iris, outlining the edges of the pupil. The muscles in the iris change in length to make the pupil smaller or larger. The amount of light passing into the eye is a powerful determiner of the size of the pupil, and the nerve pathways for this effect are well understood (*6*). This change in the pupil from its largest to its smallest size can only reduce the amount of light reaching the retina thirtyfold—quantitatively, a small contribution to the eye's enormous ability to adapt to changes in illumination—but the effect is achieved in less than a second.

Pupil size reduction also assists in changes of depth of focus for objects at different distances; there is a linear relation between the innervations to the iris muscle, the ciliary muscle, and the extraocular muscles (for convergence of the lines of sight) as the eye shifts from far to near objects. Wide individual differences exist in the magnitude of the relations between these variables. It is not known whether this pattern is fixed or can be modified through practice. A further discussion of this problem is found in (*7*), as well as in the review of current problems in neuro-ophthalmology.

The wide-open pupil, which maximizes the light-gathering power of the eye under conditions of near darkness, results in image degradation (due mainly to the effect of spherical aberration) that is not noticeable in scotopic vision because of the high degree of convergence in the rod system. Under photopic conditions, this results in a quite noticeable loss of acuity compared to what can be achieved with a smaller pupil. Campbell and Gregory (*10a*) have obtained suggestive evidence that the pupil optimizes its size at different light levels so that image quality is as good as, but no better than, the retina can utilize under the state of neural organization that obtains under the level of adaptation maintained by that light level.

The image produced by our eyes exhibits all the aberrations of an inexpertly designed optical system (*8*). One can now study this directly by observing the image in space of the retinal image of a thin tungsten wire by the method described by Flamant (*9*). The importance of spherical and chromatic aberration in degrading image quality has been examined in

this way. The relative role of light scatter in the eye media and the back of the eye grounds in degrading the quality of the retinal image has also been recently evaluated (*10*). But despite the rather poor optical image formed by the eye, the resolution of the eye as measured by subjective psychophysical methods is very high (cf. below).

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Anomalies of Refraction

Our eyes have three possible defects of focus—hyperopia, myopia, and astigmatism. Hyperopia and myopia distribute along a continuum. The distribution of these refractive anomalies is leptokurtic: the mean of the curve is very slightly hyperopic, and there are many more cases clustered around these mean values than one expects in a normal distribution. The number of cases of both moderate myopia and moderate hyperopia are much fewer than expected from a normal curve, while the number of very high hyperopes and myopes—while few—are probably somewhat in excess of expectation. Of 1,033 young men examined for National Service in Great Britain in 1957, 75 percent fell in the class 0 to 1.9 D hyperopia. Twin studies show that identical twins tend to have the same refraction, while fraternal twins reared in the same environmental conditions show no such similarity. There is also no doubt that the mean refraction of the population becomes less and less hyperopic through childhood.

While the distribution of refractive errors is leptokurtic, the distribution of each of the components of the refractive power of the eye (axial length, corneal curve, chamber depth, and lens power) is a normal (bell-shaped) curve. Sorsby (*11*) attributes the marked preponderance of emmetropia in the population to the highly coordinated mechanism involving the correlation of four normally varying components (axial length, corneal power, lens power, and chamber depth). According to this view, the outstanding characteristic of the eye as an optical system is its marked correlation of these four components. It is this correlation which generally produces emmetropic, or near-emmetropic, eyes. There is a substantial failure in correlation in, at the very most, 20 percent; these have what Sorsby calls "correlation ametropia." In addition, there are also the relatively rare ametropias due to abnormal components of refraction—generally axial length, although abnormal values of lens and corneal power also occasionally occur. Sorsby believes further that emmetropia, correlation ametropia, and component ametropia are all genetically determined. Appreciable sex differences in the prevalence of myopia have been reported (cf. appendix for a survey of refractive errors in Tecumseh, Mich.). But environment also has an effect. Monkeys (*12*) and chimpanzees (*13*) raised in a closed environment tend to become somewhat more myopic than controls.

Van Alphen (*14*) has adopted the analogy of regulatory feedback control in a theory of the origin of emmetropia and ametropia. It requires a method of detecting the direction of the refractive error, presumably by retinal feedback. The output of a comparator or a computer is fed back to "an elasticity actuator" which corrects the error and maintains emmetropia. The ciliary muscle is this elasticity regulator. In the infant eye, cholinergic stimuli predominate. If there is no adjustment of this overactivity, the tension in the ciliary muscle and choroid remains high, the pressure on the sclera is diminished, the globe does not expand, and the eye remains hyperopic. If, on the other hand, parasympathetic activity is released by control and adjustment from higher centers, the globe expands until the emmetropic state is reached; this state is then maintained by feedback of impulses between retina and ciliary muscle. Further loss of parasympathetic activity leads to further expansion of the globe and to elongation of the axis, maximal stretch of the choroid, traction and supertraction of the optic nerve, and then posterior staphyloma.

Van Alphen emphasizes the role that the higher central nervous system may play in establishing which pattern any given individual will follow. His studies show marked differences in psychological characteristics (as measured by the Rohrschach test)

between myopes and persons with normal vision. These differences increase linearly with the degree of myopia. Van Alphen believes that it is the psychological factors which facilitate the development of myopia and not the other way around, but the evidence supporting this view is equivocal. Thus the conflict of views regarding the nature of ametropia, which was summarized by Duke-Elder (*15*) in 1949, continues up to the present.

The etiology of refractive anomalies, as well as its epidemiology, must be better understood before reasonable prevention and/or cure methods can be developed. Recent therapeutic measures, including treatment of myopia by both medicine and surgery, have found resurgence of interest. Because modern methods of research technology—including biochemical, endocrinological, epidemiological, ultrasound, and high-speed computer techniques—have not been exhaustively applied to these problems and because the various active investigators are apparently not fully aware of the results of the work of others, it seems to us that the time is ripe for an international symposium on emmetropia and ametropia. It would be of value only if the best representatives of all the various theoretical and empirical points of view attended. The proceedings of such a conference could very well form the point of departure for a new phase in our understanding of the nature of ametropia.*

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Chemistry of Vision

The past few years have seen considerable advance in our understanding of the chemistry of visual pigments. Reviews by Dartnall (*16*), Brindley (*17*), and Wald et al. (*18*) can be consulted for the details. In a few words: we now know that the visual pigment molecule is made up of a chromophore attached to a protein. Professor Wald has just received the Nobel prize for his outstanding contributions in this field.

The chemistry of the chromophore has been worked out, but that of the protein is less well understood. The chromophores of all known visual pigments are aldehydes of the 11-cis isomers of vitamin A_1 or A_2. These two possible forms differ only in that A_1 has a single bond and A_2 a double bond between the third and fourth carbon atoms in the ring. Light interacts with all known visual pigments by isomerizing them to the all trans form of vitamin A aldehyde. In some invertebrate eyes—notably that of the squid—photoisomerization is the only step in the visual cycle. Other invertebrates (limulus and shrimp) and all vertebrates go through a series of color changes at the end of which the protein and the all trans vitamin A aldehyde become separate. With enzyme DPN+H and alcohol dehydrogenase, the aldehyde readily reduces to vitamin A. In the eye, visual pigments readily resynthesize in the dark. The process requires 11-cis vitamin A (presumably from the pigment epithelium), alcohol dehydrogenase, DPN+, and free unattached protein, opsin. The union of the aldehyde and the protein (opsin) is a spontaneous reaction, and it yields energy. This energy forces the oxidation of vitamin A to the aldehyde. The process continues as long as free opsin remains available.

The chemistry of these procedures has been worked out on rhodopsin, the visual pigment of the vertebrate rod. It probably applies also to whatever visual pigments exist in human and other vertebrate cones. Only one cone pigment—iodopsin taken from the chicken retina—has been extensively studied in a test tube. The differences between iodopsin and rhodopsin are defined by the differences in the protein; the chromophore is exactly the same. Although never isolated in a test tube, visual pigments of three different kinds are now known to exist in human cones. There, action spectra have been approximately defined by the method of retinal densitometry elegantly developed by Rushton (*19*) and by Ripps and Weale (*20*). For technical reasons, the methods of retinal densitometry are sufficiently sensitive to yield only the action spectra of the red and the green pigment (called erythrolabe and chlorolabe by Rushton). The action spectrum of the blue pigment, however, can be measured in atypical cases of total color blindness (Blackwell et al., Alpern et al., *21* and *22*). All three action spectra are accurately defined by Stiles' two-color, psychophysical experiments (*23*, cf. below for details). Artificial monochromacy by bright bleaching and spectral sensitivity curves of persons with dichromatic color blindness are other valid ways of estimating the action spectra of the red and green curves. All of these different methods give reasonably convergent results (*24*).

This agreement has led to a sudden increase in

* The Subcommittee on Vision and Its Disorders has since sponsored a Workshop on Refractive Anomalies, chaired by Dr. Enoch. The report of that meeting (NINDB Monograph No. 5) is available from the National Institute of Neurological Diseases and Blindness.

attempts to measure spectral characteristics of foveal cones in human and monkey retinas in vitro. From such work has come the confirmation that pigments in these cones undergo cis-trans isomerization in bleaching and that their chromophores are the same as the chromophores of human rhodopsin (*25*); therefore, their photochemistry is much the same. This suggests, moreover, that single cones contain only single pigments and that the human and primate retinas contain only three different kinds of cones: namely: red cones (λ max. about 575 nm.), green cones (λ max. about 540 nm.), and blue cones (λ max. about 450 nm.) (*26, 27,* and *28*). The information from microspectrophotometry so far is relatively meager, and the results are based only on difference (rather than action spectra); thus some lack of agreement persists about the precise wavelength characteristics of the absorption spectra of these substances (*29*). Nonetheless, the broad outlines of the three-pigment (one pigment per cone), three-cone receptor scheme are now generally accepted. It forms the photoreceptor mechanism for the trichromatic character of normal human color vision. Thus, some aspects of a controversy which has raged for over a hundred years about the nature of color vision now seem settled.

One immediate consequence is that the common variety of red-green dichromatic color blindness is now easy to understand. The protanope lacks the red-sensitive pigment (erythrolabe), and those cones which would otherwise contain it have chlorolabe. The deuteranope lacks the green-sensitive pigment (chlorolabe), and those cones which otherwise would have it contain erythrolabe instead. Probably both see the red-green range of the spectrum as yellow (Graham-Hsia et al., *30*). The retinas of the anomalous trichromats are in some ways similar—protanomalous containing little or no measurable erythrolabe, deuteranomalous containing little or no chlorolabe. It is still not clear why the anomalous set the red-green mixture to match yellow (in the anomaloscope) in the way they do. One possibility—that the density of the remaining pigment causes a distortion due to self-screening—is probably not correct. Apparently, anomalous trichromats contain small amounts of other pigments which have, so far, not been detected by retinal densitometry. Their nature may be easier to define by the two-color method than in other ways, but more work on this question is needed.

The account just given may be an oversimplification. The pigment loss in many dichromats of the red-green variety may not be absolute, since they seem to show a residual red-green discrimination under special testing conditions (*30a*). In evaluating this, however, we need to be certain that the subjects were true dichromats and not just severe anomalous trichromats; and this distinction is not easy to make without rather extensive documentation. Some varieties of color vision defects also clearly involve injury to the head rather than defects within the eye (*30b*).

While this outline of knowledge about the receptor basis of color vision shows how well accepted the receptor mechanism of the three-color theory (postulated by Young, Helmholtz, and Maxwell) has become in the last few years, it must be emphasized that the evidence from cellular electrophysiological studies points in the direction of an opponent color scheme proposed by Ewald Hering (cf. below). Before going into this question, however, we must examine the status of knowledge of the process of visual excitation. This, in our television-vision analogy, represents the stage where the optical image in the camera is coded into electrical signals.

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The Nature of Excitation

The question of how photochemical events in the rods and cones are translated into nerve signals is the most fundamental of all the biological questions in vision physiology. We know very little about this, but our understanding of retinal excitation is, nonetheless, better than our understanding of excitation elsewhere. We know that the outer segments of the retinal rods and cones are the sensory organelles where the light quanta are absorbed. It seems almost certain that the absorption of a single quantum of light by a single molecule of rhodopsin can excite a single retinal rod (*31*) and that excitation of only a very few rods is necessary for vision to occur (*32*).

The diameters of the sensory organelles of the rods and cones are of the same order of magnitude as the wavelength of light. Therefore, they show wave modes, as Enoch (*33*) has demonstrated. In a wave mode, energy is nonuniformly distributed, and that distribution and the efficiency of transmission are influenced by such factors as wavelength, polarization, optical density, and the angle at which the light is incident at the receptor.

This last is related to a phenomenon first described by Stiles and Crawford (*34* and *35*). They found that cone receptors are most responsive to light entering along their axes and less and less sensitive to light incident at increasingly oblique angles to their axes. In addition, there are changes in the perceived hue and saturation of colored stimuli for oblique angles of incidence (*36*). In rods, directional sensitivity is not found psychophysically for angles of incidence achievable at the retina through normal pupillary apertures (*37*). Enoch (*38*) has found both rods and cones to be more highly directionally transmissive as waveguides than might be suggested by visual testing. In addition to shape and dielectric factors, which give rise to waveguide properties, there are other directionally oriented elements in retinal receptors—the mitochondria in the inner segment of the cell (often studied by their directional scattering properties), and the laminated membrane plates in the receptor outer segment, and the photosensitive pigments contained in these plates. The pigment elements are oriented so that maximum absorption results when energy is transmitted directly along the cell axis.

In the vertebrate rods and cones there are no convincing recordings of conventional nerve impulses (action potentials) despite exhaustive attempts to obtain them. The recent microelectrode recordings from monkey eyes have detected a very early (d.c.) electrical change evoked by light (*39*). This response can even be recorded from the all-rod retina of the rat with gross electrodes (*40* and *41*). It has, then, the action spectrum of rhodopsin while, in the all-cone retina of the ground squirrel, it has the action spectrum of the cone pigment of that eye. It varies in magnitude linearly with the number of molecules of visual pigment which absorb light quanta. It persists at very low temperatures (−35° C.), but evidence exists that it cannot be produced in the original photochemical reaction in which rhodopsin is converted to prelumirhodopsin. Unlike all other known biological potentials which have been studied, it does *not* depend upon the ion distributions on the two sides of a biological membrane and on the selective permeability of that membrane to ions (*42*).

In invertebrate photoreceptors, these early receptor potentials have, so far, not been observed. In these, dim light stimuli evoke miniature (d.c.) potentials which vary in all-or-none fashion (*43*). Their frequency is consistent with the idea that each absorbed light quantum produces one miniature potential (*43*). As light intensity increases, these potentials merge to form a steady depolarization, which lasts as long as the light is on. This generator potential is produced by the same cells which contain the visual pigment (retinula cells, *44*). Action potentials —the nerve impulses carried to the brain—are produced by the next cell in the chain, the eccentric cell (*44*). An important theoretical model for the mechanism producing the generator potential in the limulus eye has recently been developed (*45*). This model quantitatively accounts for the fact that dark adaptation increases sensitivity and slows the generator potential response, while light adaptation decreases sensitivity and hastens the response; it also predicts the form of the generator potentials for light of a variety of waveforms and stimulus intensities. The importance of this model for our understanding not only of cellular events in the limulus photoreceptors, but of dark and light adaptation in the human retina, has been recently emphasized by Rushton (*46*).

In slices of squid retina dissected in the dark, Hagins, Zonana, and Adams (*47*) have succeeded in mapping the changes in electrical fields in the rod outer segment when excited by a small localized point of light. These experiments suggest that light produces some local electrical change which allows

current to flow into the outer segments within a few microns of the point where the quanta are absorbed. The changes of voltage described here differ from the early receptor potential in that they presumably depend upon membrane permeability to specific ions and a concentration gradient of these ions in the same way that other biological potentials do.

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Adaptation

The human eye has the amazing ability to adapt to lights over a range of about 10^{10}. Following exposure to bright lights, it takes over 30 minutes in the dark for the eyes to gain maximum sensitivity. The first 5 to 15 minutes are dominated by recovery of the cones; the rest, by the recovery of the rods. The rod monochromat (in whom cones are so few that they do not obscure the early part of rod dark adaptation) reveals a change in sensitivity over about 10^7 for rods during dark adaptation (*46*). Retinal densitometry shows that, in this case, there is a linear relation between the logarithm of the light intensity required for threshold visibility in the rods and the amount of bleached rhodopsin in the rod. A similar relation has been demonstrated in the rat retina, both by bleaching experiments and by raising rats on vitamin A acid, which provides all necessary nutrition except rhodopsin for the rat (*48*).

Light adaptation does not produce its decrease in sensitivity by elevation of the number of quanta necessary to excite the rod. On the contrary, the sensitivity of the retina depends upon the state of rhodopsin bleaching in *all* the rods which feed into a common pool; it is the state of excitation of the pool which determines the threshold. Thus, the thresholds of unbleached rods can be elevated by bleaching their neighbors, provided only that all feed into a common excitation pool (*49*). There is a continuous signal to the pool from all its rods, indicating the amount of unregenerated rhodopsin. This forms the dark light of the retina and adds linearly to real light in the determination of threshold. The dark light of the retina matches the positive afterimage in brightness when both are stabilized on the retina (*50*).

It seems that the relation between the concentration of rhodopsin and the light intensity for threshold vision is logarithmic. This finding, which differs significantly from an essential ingredient in Hecht's photochemical theory of vision, has led to a search for a mechanism yielding a logarithmic transformation. A strong case has been made by Rushton (*46*) for the adaptation of the Hodgkin-Fuortes model of a parametric feedback system. Feedback models of retinal action have been put forward before (*83*), but the merit of Rushton's formulation is that its quantitative predictions fit his findings quite accurately (*50a*). However, certain discrepancies remain. Spatial summation (*46*), spatial inhibition effects (*50b*) in the human dark-adapted rod retina, and the temporal factors of summation need to be fitted into the feedback model.

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The Cell Physiology of the Retina

The R membrane is a barrier of high electrical resistance between the choroidal circulation and the visual cells. Both morphological (*51*) and physiological (*52*) consideration suggest that the pigment epithelial layer is the site of this barrier. There is a large difference in electrical potential between the two sides of this membrane. With a corneal electrode, the difference is about 5mV. with the retina positive. The voltage is useful as an objective way of recording eye movements. Reductions in the magnitude of the voltage associated with diseases of the retina, pigment epithelium, and uvea can be of diagnostic value. Slow changes in the potential are evoked by light and by pharmacological agents. The nature of the transretinal current, which gives rise to these potential changes, has not yet been clearly elucidated. Analogies to the frog skin have been drawn (*52*), but the evidence supporting such analogies is not conclusive.

In addition to these very slow changes, the corneal electrode also records changes in potential evoked by light, which are considerably faster. These changes—the electroretinogram (ERG)—are among the oldest known bioelectric phenomena. The enormous literature as of 1940 has been reviewed (*53*). More recent work and microelectrode studies have tended to localize the retinal source of the ERG. The difficulties in interpretation are large (*54*), but it seems likely that the *b* waves (of the ERG) originate in the same layer of the retina that contains bipolar cell nuclei (*55 and 56*). The results for the *a* waves of the ERG are not as clear. In mammals, it seems likely that they originate in the layers containing the nuclei of the rods and cones (*56*); but in cold-blooded vertebrates (frog), both *a* and *b* waves likely originate in the same part of the retina.

The ERG remains a tool for study of the mass response of the retina instead of individual cell activity. Thus, ERG's as clinically studied give a rod-dominated response because there are about 20 rods for every cone in the human retina. However, recently improved means of distinguishing very weak electronic signals have now made it possible to record local ERG responses to relatively weak light flashes which are seen against high-background light levels (*57*). In addition to the fundamental promise these methods hold for studying basic retinal physiological process in the human eye, they may make possible a way of measuring the visual field without subjective responses.

Microelectrode studies of cellular events at the retina are also of major importance in understanding questions about the code of messages from the photoreceptors to the brain. A microelectrode can penetrate a retinal cell which shows slow (d.c.) changes in the potential difference across its membrane after illumination. Such cells were first thought to be photoreceptors, but they are most likely either bipolar, amacrine, or horizontal cells, or glia (*55*). Two varieties of such cells (now called *S* cells) are described as: (*a*) Those which hyperpolarize only to light irrespective of the wavelength of illumination (luminosity or L cells) and (*b*) those which hyperpolarize to some wavelengths but depolarize to others. Two varieties of the latter have been described, depending only upon whether the antagonistic hues are red-green or blue-yellow. The *S* cells characterize exactly the sort of behavior required of physiological processes associated with the theory of color vision proposed in 1874 by Ewald Hering. (A translation of Hering's remarkable monograph has just recently appeared (*58*).)

S potentials are graded; they vary in magnitude with the intensity as well as the wavelength of the light. Thus, they are quite different from the conventional all-or-nothing responses of the action potential which is known to be the basic element of the signals connecting the peripheral and central nervous systems. In vertebrate eyes, such signals have been recorded only from retinal ganglion cells. Studies of these phenomena by Granit (*59*) and Hartline (*60*) began before the Second World War. For this research and subsequent investigations Granit and Hartline have recently been awarded the Nobel Prize for Medicine. They showed that many such cells are spontaneously active in the dark and that increased illumination of the retina may either increase (*on* cells) or decrease the rate of action potential production. Similarly, decreasing illumination may either increase (*off* cells) or decrease the rate of firing. The way the rate of firing varied with light intensity was worked out in these early experiments, as were the techniques for outlining the "receptive field," the region of the visual field in which change in the visual stimulus may influence the activity of a given ganglion cell.

Barlow (*61*) showed in the frog, as did Kuffler (*62*) in the cat, that different parts of the receptive field excited increased activity of a ganglion cell. Such activity can be greatly reduced by simultaneously illuminating the center and the edge of the receptive field. In fact, exactly the same effect has been described in the lateral eye of the invertebrate limulus

(*63*). The simplicity of this latter preparation allows a much more exhaustive analysis and more precise mathematical formulation of the physiological processes involved. The illumination of one limulus ommatidium increases the activity of its eccentric cell, and this is reflected by an increase of the action potential in its optic nerve fiber. Simultaneously, nerve filaments from this eccentric cell carry action potentials to the eccentric cells of adjacent ommatidia, inhibiting their rate of firing to illumination. The influence of adjacent eccentric cells on each other is one of reciprocal, mutual (backward) inhibition. These phenomena represent physiological processes at the cellular level which correlate precisely to the psychological experience that a bright light seen against a bright background appears dimmer than it does when seen against a dark background (simultaneous brightness contrast, *64*).

It is evident that even at the level of the retinal ganglion cells (which, so far, are the most distal cells from which conventional nerve impulses can be recorded), a good deal of "coding" and "processing" of the information contained in the visual stimulus has taken place. In the frog, a number of different varieties of ganglion cells can be described according to their morphology, on the one hand, and to the kind of visual stimulus which will be most successful in exciting them, on the other (*65*). Comparable processing occurs in other vertebrates. Of special interest are the ganglion cells of the rabbit retina. Some of these show sensitivity of movement in one given direction (*66*). Species differences no doubt play an important role. Retinal ganglion cells in eyes with color vision, at least, send coded signals to the brain which supply information about the wavelengths of the light which excites the retina (*67*). These cells are characterized by an ability to increase firing at *on* and decrease firing at *off* in response to some parts of the spectrum, while showing the opposite (decreased firing at *on* and increased firing at *off*) response for other parts of the spectrum. Antagonistic wavelengths of this sort can be found for red *vs.* green hues in some cells and yellow *vs.* blue for others. Evidently, the eye speaks to the brain in a language already organized and interpreted. Ganglion cells have a clear ability to discriminate—an ability which is not surprising to find in the animal as a whole, but is rather startling in single units of the retina.

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Physiology of the Visual Pathways

The essential information about responses to light stimulation of single cells in the visual pathways has only begun to be accumulated. Studies to date are best on the so-called specific (or primary) pathways, although cells in the reticular nonspecific pathways are also activated by light excitation of the retina (*68*). In the direct (primary) nerve pathways from the eye to the brain, the first (thalamic) station is in the lateral geniculate nucleus. Here, nerve fibers from the temporal half of the retina of the ipsilateral eye and the nasal half of the retina of the contralateral eye converge. At this level, the nerve fibers which pass to the midbrain to activate the nerve centers for the pupil light reflex have already split off. The lateral geniculate nucleus is laminated into six-cell layers, the two most ventral layers containing much larger cells than the others. At this level, the amount of connection between nerve fibers from the two eyes is trivial, and successive layers support synapses of fibers from separate eyes. Beginning at the most dorsal layer, the synapses of fibers are exclusively from the contralateral eye; the second layer contains the synapses from fibers only from the ipsilateral eye, and succeeding layers contain contralateral, ipsilateral, ipsilateral and contralateral syn-

apses, respectively. Thus, each eye is related to three layers in each lateral geniculate nucleus, but, contrary to earlier speculation, these three layers apparently have no relation to physiological responses of the three-color cone systems of the primate retina.

Data are now available on how lateral geniculate cells respond to light (*69*). In general, two kinds of cells are found: (*a*) Spectrally nonopponent cells, which respond either with a decrement or an increment in firing rate to lights of all wavelengths, and (*b*) spectrally opponent cells, which respond to some wavelengths by an increase in firing and to other wavelengths by a decrement in firing. The first class is very sensitive to small changes in intensity but not at all sensitive to shifts in hue (provided intensities are equated). The second class responds in exactly the opposite way: it is insensitive to intensity shifts and very sensitive to hue changes. These latter are much more numerous than the "brightness" cells in the monkey, but not in the cat. The antagonism between wavelengths in such cells is red *vs.* green in some cells (the more numerous) and blue *vs.* yellow in others. Studies of this sort so far have been published only for diffuse retinal illumination. Promising data are currently being accumulated using more discrete stimuli, and these should provide much basic information about physiology of form perception and many other complex perceptual processes.

The receptive fields of lateral geniculate cells are more or less circular, as are those of retinal ganglion cells. Evidently, several such adjacent cells with overlapping fields converge on single cells in the visual cortex. The receptive field of such a cell is usually oblong (*70*). It is characterized by sensitivity to slits of light and is enormously sensitive to the direction of orientation of the slit. Usually such cells are relatively unresponsive to diffuse retinal illumination. Such cells are classified as "simple." "Complex" cells respond vigorously to movement of the slit in one direction and little, if at all, to movement in the opposite direction. They show many properties similar to those of rabbit ganglion cells (*66*).

Most cells in the cat's visual cortex are excited by stimulation of either eye. In kittens raised with one eye visually deprived, however, this is not at all the case (*71*). These observations are important for the theory of strabismus amblyopia. The experiments of Hubel and Wiesel show that vertical columns of the visual cortex are arranged with receptive fields having similar orientations. Adjacent columns have cells with receptive fields arranged with slightly different orientations. In higher areas of the brain (visual cortexes 18 and 19), simple cells are no longer found; complex cells are more numerous (*72*). Moreover, two varieties of "hypercomplex" cells now appear. Lower order hypercomplex cells respond to oriented lines which are terminated within the receptive field (corner detectors). These behave as though they received inputs from two complex cells, one exciting and the other inhibiting. Higher order hypercomplex cells respond to lines in either of two orientations 90° apart as though they received inputs from a large number of lower order hypercomplex cells. This brief description cannot adequately summarize this work, but such microelectrode studies provide clear understanding of many of the properties of the physiological basis of the perception of form at the cellular level.

The way the visual cortex participates in learning experiments has recently come under study. "Split-brain animals," in which the connection between the two sides of the brain are severed, are taught a visual discrimination with one eye and tested for retention by exposing the other eye to the stimulus. When the optic chiasm and corpus callosum of the two semihemispheres are severed, pattern discrimination fails to transfer, but brightness discrimination does transfer. The effect is, however, dependent on the training method as well as on the experimental animal. Useful information may soon be forthcoming from experiments of this kind on the relative roles of different nerve pathways and cortical brain areas in visual learning tasks, but so far the results are only suggestive.

Amphibia and teleosts show a remarkable ability to regenerate the optic nerve and retina after the optic nerve has been cut. These regenerated nerve tissues are functional, and such animals see very well. Experiments have been carried out in which, after the optic nerves are cut, the eyes are rotated 180°. When vision returns, these animals see everything upside down and will even starve to death diving to the bottom of the aquarium to find food sprinkled on the surface of the water. Physiological experiments currently underway promise to show how each single regenerated nerve fiber manages to find its way to the proper connection with its severed end, even when the eye has been rotated, and how visual learning fails to influence these mechanisms, even when survival of the animal is at issue.

For some years, the electroretinogram has been the only nonmuscular visual response to light recordable from human subjects. During the past 7 or 8 years, it has proved possible to record evoked potentials from scalp electrodes which clearly correlate with photic input. To do this, it is necessary to use a computer of average transients, or similar device, and repetitive stimulation. The computer increases the signal-to-noise ratio in the average of many responses so that the average response shape, latency, etc., is clearly discernible, while individual responses are not. It is difficult to assess the full potential of this method at present: it is easy to use but difficult

to interpret and may very well be useless without proper controls (*72a*).

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Psychophysics

Good psychophysical measurements on human eyes have been made for at least 150 years. The summary of the early work by Helmholtz (*1*) is still a very useful reference. The important contributions of psychophysics to our understanding of visual physiology, particularly in the first 35 years of the present century, has been elegantly summarized by Hecht (*73*). More recently, the rather closely written monograph of Brindley (*17*) and the more voluminous summary by Pirenne and Marriott (*74*) bring the subject up to date.

Throughout the 19th century and well into the 20th, psychophysics was, for all practical purposes, the only way of studying vision physiology. More recently, biochemical and electrophysiological methods have provided very valuable new insights, but much information continues to come from the older techniques. It is the physiologist's ability to build electrophysiological and biochemical experiments on the wealth of information provided by a century and a half of good visual psychophysics that has made the understanding of the physiology of visual perception much more advanced than any other aspect of the neurophysiology of behavior. Modern psychophysics of vision is important not only for what it tells us directly about the physiology of vision (for example, in dark and light adaptation), but also because it enables the biochemist and electrophysiologist to ask meaningful questions. A good deal of the knowledge already described in this report has been and is being obtained by psychophysics; therefore, only those aspects not previously summarized will now be surveyed.

1. *Color Vision.*—Normal human color vision is trichromatic (*17*). This means that, given any four lights, it is always possible to place two in one half and one in the other and, by adjusting the intensities of three of the four lights, to make the two halves of the field indistinguishable to the eye. Measurements of this kind were made quantitatively by Helmholtz and by Maxwell and have grown more elaborate with modern developments in spectroscopic optics. The small-field measurements are summarized in a monograph by Wright (*75*). More recently, measurements with both 2° and 10° fields have been completed by Stiles and Burch (*76, 77,* and *78*). So far, good measurements have been made only on normal eyes, and the way various kinds of retinal anomalies may influence the color matches that people make has scarcely been examined at all (except for the classical kinds of red-green color defectives). Work of this kind may be valuable both for understanding the nature of the retinal abnormality and for normal physiology.

Quite a different kind of measurement of color vision has been developed by Stiles (*79, 80,* and *81*). A test flash of one monochromatic waveband is seen either on a dark background or on a background of varied dominant wavelength and luminance. Under such conditions, the thresholds for the rod mechanism π_0 and for each of the cone mechanisms π_1, π_4, and π_5 follow the Weber-Fechner relation quite simply. For each mechanism the threshold is lowered in proportion to its sensitivity to the background. Four independent increment threshold curves coexist, and the threshold under certain conditions is predominantly determined by the lowest increment threshold curve under that condition. These facts have proven to be very powerful tools for studying color vision. They allow exact measurement of the spectral sensitivity of the rods and observation of their saturation at a level when only about 10 percent of their rhodopsin has been bleached (*82*). Furthermore, they can be used to measure the spectral sensitivities of each of the cone mechanisms (*79*), and, indeed, the measurements have been remarkably successful in predicting (almost 20 years before the facts were obtained) the action spectra of chlorolabe and erythrolabe (*19*) and of the blue cones (*21* and *22*). This impressive achievement has only slowly become recognized. A recent review by Boynton is of interest (*83*). Wald, in particular, has recently been extremely diligent in applying Stiles' techniques to color defectives (*29*). DeVries (*84*) recognized the remarkable possibilities inherent in such experiments almost 20 years ago.

Of course, human color vision is much more than the differential absorption of light quanta by three overlapping, but narrow, band visual pigments—one each in three different kinds of cones. The most convincing recent demonstration of this fact has

been made by Land (*85*), who shows how effective only two degrees of freedom can be in evoking a variety of color experiences when they are produced by photographs of the everyday visual world and not merely by a homogeneous photometric field. Although, as pointed out by Land and by others (*86*), a variety of phenomena are important in producing these effects, phenomena of color contrast are especially relevant.

As was emphasized above, we know a good deal about the physiological basis of brightness contrast based upon mutual, lateral inhibition of different parts of the receptive fields of retinal ganglion cells (*87*). But color contrast is a different matter—we know virtually nothing about the physiological basis of *it*. One recent suggestion is that the individual cone mechanisms exert lateral inhibition on members of their own kind in adjacent retinal areas and are as independent of the excitation of the other kinds in these areas as they are in Stiles' two-color experiment. Thus, a gray square on a red background looks blue-green because the red cone mechanisms excited by the gray square are inhibited by the red cone mechanisms excited by the background, while the blue and green cone mechanisms are not similarly inhibited (*88*). Electrophysiological evidence for such effects has not yet been forthcoming. Still less is known about the physiological basis of other aspects of Land's demonstration, including the problems of color constancy, color adaptation, and memory colors.

2. *Time Resolution.*—The eye is relatively poor at detecting small differences in the visual stimulus from one moment to the next. This has been studied most extensively by noting the maximum rate of alternation in a periodic square wave sequence of light flashes which is just seen to flicker (the critical flicker frequency, c.f.f.). Measurements of c.f.f. have been made at least since about 1740, so by now the way it is influenced by a variety of variables—physical (light intensity, background intensity, area, on/off ratio, dominant wavelength), psychological, pharmacological, and pathological—has been extensively examined. Fortunately, an annotated bibliography of references up to 1952 has already been published (*89*). The most exciting development in this field since 1952 has been the application of linear systems' analysis theory to the visual perception of flickering stimuli introduced by the Dutch electrical engineer, de Lange (*90* and *91*). He used light varying in time sinusoidally around a mean intensity at various frequencies. At each frequency, the smallest amplitude sine wave which permitted flicker perception was measured. The early results show many characteristics of a linear, low-pass filter. The more recent experiments, however, suggest that for high light intensities there is a clear decrement of flicker perception at the low, as well as the high, frequencies, with the suggestion of "resonance" frequency in the region of 10 cycles per second. The influence of many experimental variables on curves showing the threshold modulation at various frequencies is now receiving wide experimental attention. A summary of work excited by de Lange's application of Fourier's methods to flicker perception has now been published (*92*), and interested readers can consult this for the numerous details.

The processing of time by the visual system is also being investigated by a number of techniques not involving flicker. These include intensity-time relations at threshold and above for single flashes, experiments on subjective simultaneity, and a wide variety of experiments involving interactions between two flashes (*92a*). The latter have been interpreted as measuring visual masking effects, transient adaptational effects, and short-term visual memory, depending upon the exact experimental conditions used (*92b*).

3. *Space Resolution.*—The eye is much more effective in its ability to resolve minute differences in spatial position than it is in its ability to resolve time fluctuations of the visual stimulus. Reciprocals of spatial resolution thresholds (in minutes of arc) are measurements of spatial sensitivity or visual acuity, and the human eye's acuity under optimal conditions is truly remarkable. Because of practical importance for 19th century optical astronomers as well as for clinical medicine, good psychophysical measurements of visual acuity are also very old. Consequently, much is known about the experimental (stimulus intensity, contrast, duration, dominant wavelength, target distance, and background intensity), physiological (region of the retina excited, refractive defocus, pupil size, adaptation level, etc.), and psychological variables which influence visual acuity. A very clear summary of such information has just recently appeared (*93*).

An important question which pervades this literature is: How can the resolution of misalignment of two long lines (vernier acuity) be much higher than the most reasonable estimates of the "graininess" of adjacent foveal cones? The discrepancy may be as large as fivefold, although more recent estimates of the diameter of foveal cone outer segments tend to be smaller than the classical morphology literature suggests. One common idea requires some "neural interaction" based on the fact that, even under the steadiest fixations, the eyes are never motionless. Hence, neither is the image on the retina, any given part of which is constantly exciting different sets of foveal cones. We now know that these ideas are wrong. Modern contact lens techniques have made possible optical arrangements for stabilizing the image on the retina during eye movements (*94*).

Such methods do not reveal the decrement in visual acuity predicted by eye movement theories of the superiority of visual acuity to that expected from the "grain" of foveal cones. Other factors are undoubtedly important—particularly more complex psychological ones—since performance with long lines greatly exceeds that for shorter ones. (Purely optical considerations tend to treat the line *width* as the only relevant variable.)

One unexpected outcome of the stabilized image experiments is that, when viewed for longer than a few seconds, the images of high contrast borders stabilized on the retina gradually fade. Disappearance takes about 5 seconds. Although fine eye movements during steady fixation cannot account for vernier acuity superior to that expected, they are essential for continued clear viewing of visual stimuli.

There is a severe decrement in visual acuity as one moves away from the point of fixation. This fall is very closely related to the relative proportion of the area in the striate cortex topologically congruent with different parts of the visual field. While the study of eye movements per se is beyond the scope of this report, it needs to be emphasized that there is a close relation between the extraction of information from the peripheral visual environment and eye movements. Visually guided behavior as dependent upon peripheral vision is an important and relatively unstudied problem. Patients with constricted visual fields represent a group particularly handicapped by the dearth of such studies and a fruitful source of fresh experimental insights about these problems.

As is the case in temporal resolution, modern linear systems' analyses have recently also been applied to visual acuity tasks. The pioneer was Schade (*96*). A sine wave grating can be imaged on the retina and its amplitude varied at each of a variety of frequencies (mean retinal illuminance held constant) for threshold resolution. By using interference fringes, the method can be made to circumvent the eye's optics and, by viewing in this way as well as with the conventional methods, the roles of the optics of the eye and of the "retina-brain" can be separately evaluated (*97* and *98*). The relative roles of these components are still not exactly specified. Westheimer's measurements suggest that the resolving power of the retina-brain is essentially the same as the best the eye can do using its own optics. Campbell and Green regard the retina-brain as providing the limit for pupils $\leq$2 mm. and the eye's optics as providing more and more limitations as pupils become larger and larger. Their findings suggest that spherical aberration is an important contributor to decreased visual acuity, but diffraction is not. Essential information from microelectrode studies on retinal ganglion cells of the cat may soon appreciably aid our understanding of the physiological basis of visual acuity.

The clinical measurement of visual acuity may well involve information and communication, theoretical aspects over and above simple resolution.

Under optimal conditions, the binocular visual acuity is about $\sqrt{2}$ times better than that of either eye alone. This is more than one expects on the basis merely of "probability summation," and the reason for this effect is far from clear.

4. *Space Perception.*—Binocular vision physiology is also covered in the report on neuro-ophthalmology, and so this phase of the review will be short. Physiological means of studying binocular vision on animal eyes are traditionally limited in the validity of the extrapolation to man because the extent of overlap of the visual fields of the two eyes in man is only found in very few primates. Nonetheless, the experiments of Hubel and Wiesel on the cat show that an amazingly high percentage of the cells in the visual cortex are, in fact, driven by retinal excitation in either eye. For this reason, it is possible that similar studies on monkey eyes may begin to provide ideas on how the retinal signals from the two eyes in man combine. So far, inferences along these lines are drawn only from psychophysical experiments on normal man. For good reviews of the current knowledge in this classical field of psychophysics, see recent monographs by Ogle (*99* and *100*).

Briefly, two eyes provide a facility for ready perception of relative depths of objects in our visual field. This facility (binocular stereopsis) improves as the objects concerned are brought closer to the eyes so that, at very close distances, the ability of a person with a properly coordinated pair of eyes to make fine discriminations among differences in distance is remarkably superior to that of a person with only one eye. This facility (the major difference in perceptual ability of a monocular compared with a binocular observer) is apparently natively given and probably not very adequately trainable in binocular observers. Stereoscopic thresholds are influenced by a large number of stimulus characteristics (light intensity, region of the field, area of targets, exposure duration) and observer characteristics (including, foremost, separation of the eyes). The role of magnification of the image of one eye on binocular space localization has been examined and its clinical importance in evaluating binocular discomfort extensively evaluated. Aniseikonia (a disparity in perceived magnification in the two eyes) is an optical disorder which may be treated appropriately with suitable spectacle and contact lenses. It is a real source of difficulty in unilateral aphakia (absence of the lens in one eye) but also has relevance in other

varieties of refractive anomalies. Its importance has been summarized by Ogle (*99*).

Stereoscopic binocular vision is best studied by presenting slightly different targets to the two eyes in a stereoscope or other viewer which allows presentation of a separate pattern to each eye. Recently, Julesz (*101*) has stimulated a good deal of new interest in this phenomenon by generating stereogram images with random dot patterns by a computer. These targets are devoid of many (but not all) of the familiarity "cues" of ordinary stereograms, and, thus, they allow a more careful analysis of the role of contours in binocular depth perception. The method has promise of providing new information about a very old problem.

Of course, space perception (even relative depth perception) involves much more than binocular stereopsis. A number of other variables are important, particularly for distances larger than a few meters, where the binocular parallax produced by the lateral displacement of the two eyes becomes trivial. These so-called "empirical cues" for space perception include visual size, accommodation, convergence, overlay, perspective (both aerial and linear), shadows and light areas, parallax with head displacement, and height, as well as certain binocular empirical factors. Almost all of these variables were known to early painters (*102*). We know virtually nothing about the psychology of these phenomena, much less about their physiology. Even the extent to which they *are* empirical requires better documentation than is available so far.

5. *Psychology.*—It seems appropriate to conclude this report with a brief description of what is known in visual psychology. This is necessary because the borderline in vision between the physiological and the psychological, while never very sharply drawn, has become even more smudged by the microelectrode studies on single units in the brain. The classical literature is very well summarized in a review by Berliner (*103*) published over 15 years ago. Many of the problems there discussed—such as mechanism of contour formation, Mach Bands, brightness contrast, movement perception—are beginning to yield to the physiologist's microelectrode, and it is particularly informative to reread Professor Berliner's monograph in the light of the most recent physiological experiments. However, many problems of visual perception still elude physiologists. Notable among these are problems of visual illusions, constancy, adjustment, and visual learning.

The tendency to perceive objects in the same way under a variety of different stimulus conditions is known as constancy. Size constancy—the way we perceive distant objects much larger than (and near ones much smaller than) the size of the retinal image would lead us to do—is only part of the complex problem of the visual perception of size and distance (*104*). Psychophysical experiments on the relative roles of accommodation and vergence in perceived size are still very fruitful.

Besides size constancy, there is shape constancy, brightness constancy, and color constancy, all of which have similar properties. The constancies are examples of a more general problem of perception: namely, the abstraction of invariances from the visual environment. Current research and theoretical treatment (c.f. Land's treatment of color constancy in reference *85*) tend to evaluate the constancies in isolation, but a much more heuristic theoretical treatment should come from a unified treatment of the phenomena of constancy as such.

One remarkable characteristic of visual perception in man is how quickly he adjusts to environmental change. Very early in the present century, certain psychologists wore prisms, which turned their visual world upside down, and carefully studied the way they adjusted themselves to this reversed visual space (*105*). These experiments—while out of fashion for a long time—have now become popular again. These recent experiments are now asking much more meaningful questions. They show that a person's (or an animal's) movements change what he sees. By tampering with the feedback loop, it is possible to evaluate its importance in maintaining space orientation. A readable summary of work with prisms has been recently published (*106*).

Work has also progressed on other aspects of adjustments to the visual world—for example, prolonged wearing of color glasses, blue for the right half of the visual field, yellow for the left. Color adaptation occurs very readily, so that shortly the two halves of the field appear to be the same color. When the glasses are removed, a transient adjustment in the opposite direction takes place. A remarkably similar adjustment to the prolonged wearing of an afocal magnifying lens over one eye by normal observers has been studied (*99*). This is more easily quantified (with the space eikonometer) than most other such adjustment experiments, and the method could potentially bring a certain amount of order to an area of experimentation which has, so far, been largely descriptive and qualitative. The similarities of these experiments, however, have generally gone unnoticed. Of special interest in all such adjustment studies is the way our capacity changes with increasing maturation.

This summary of some of the major issues in visual psychology is necessarily incomplete. Whole books have been recently published which summarize much more adequately—albeit still incompletely—the current state of knowledge in this field. The reader is referred to them for a more complete analysis of some of these problems (*107, 108, 109,* and *110*).

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SOME OF THE NOTEWORTHY RECENT ADVANCES

There is no other field in biology at the present time in which there is such a satisfactory understanding at the cellular level of so many diverse aspects of human behavior. This one fact is the best summary of the current status of research on the physiology of vision. It is the main reason that vision research today is on the verge of enormous breakthroughs which promise to shed considerable light, not only on how we see, but on the more general problems of the nervous system, including excitation, learning, thinking, motivation—problems which have puzzzled man since he first began to think.

It seems to us that this is due to the modern techniques that have been brought to bear at the cellular level on all the different parts of the visual system. These methods include microelectrodes, enzyme chemistry, electron microscopy, microspectrophotometry, and retinal densitometry, to name only a few of the most obvious, recent developments. But since these techniques can and have been used in a variety of other biological fields, why has their employment been so especially fruitful in the application to vision? One reasonable explanation is that

modern cellular physiology of vision begins against a century-and-a-half background of good, psychophysical measurements of visual behavior. The cell physiologists ask the right questions about the retina, for example, because Thomas Young, Ewald Hering, James Clerk Maxwell, Hermann von Helmholtz, Selig Hecht, W. S. Stiles, and many, many others showed by exhaustive psychophysical experiments which questions are most likely to yield the most heuristic answers. In no other field is the psychophysical data so large and so meticulously studied for so long a period.

In the last few years, we have gained—through the efforts of Wald, Dartnall, Crescitelli, and others—a deep understanding of the sequence of chemical events which follows the absorption of a quantum of light by a molecule of rhodopsin in the retinal rods. Furthermore, we know something of these events in the visual pigments of the retinal cones as well, although test tube studies on them are few. Rushton has shown that separate red and green visual pigments exist, and psychophysical studies on color blinds reveal the blue pigment as well. Microspectrophotometry in single foveal cones in human (and monkey) eyes amply confirms these observations and suggests furthermore that the different cones have different pigments (one cone—one pigment). Color vision begins at the receptor level in much the way Thomas Young said it did in 1802. Many of the forms of color blindness are very simply and easily explained by these new facts. The process of color vision, of course, is more than excitation of cones. Ganglion cells of the fish retina and cells in the lateral geniculate body of the monkey do not behave at all like the Young-Helmholtz theory predicts. These cells fire to one spectral waveband and are inhibited by its compliment. Qualitatively and quantitatively, these behave in exactly the way predicted by Ewald Hering's (1872) opponent color vision theory.

Lettvin and Barlow, with collaborators, describe ganglion cells in the retinas of frogs and rabbits, respectively, which have already carried out important operations on the signals which are dispatched to the brain from the retina. These cells permit detection of curved lines, of straight lines, of edges, of movement in particular directions (and not in others), and so on. Cellular studies with microelectrodes in the visual cortex by Hubel and Wiesel have made it possible to observe different stages in the elaboration of the complex process of form and movement perception. The familiar process of simultaneous brightness contrast is readily observed at the cellular level in the compound eye of the horseshoe crab limulus. The microelectrode studies of this lateral inhibition by Hartline and Ratliff at the Rockefeller Institute have provided quantitative laws of synaptic organization which transcend the simple arthropod eye and extend to nervous interaction, both vertebrate and invertebrate, throughout the animal world.

FUTURE PROSPECTS AND RECOMMENDATIONS

The record is a good one, and it is the support of the NINDB which has made much of it possible. But it would be a real mistake to stop or to slacken at this point. We are on the verge of finding how it is that absorption of a single quantum can excite a single rod, and, when we know this, we will have begun to close the gap between man and his external world. Understanding of other forms of sensory excitation will soon follow and then, perhaps, of excitation throughout the nervous system as well. How do the signals from the red, blue, and green component cones become transformed so that, when they reach a single, opponent ganglion cell, it fires to yellow and becomes inhibited by blue? What is the nature of the code of the signals connecting the sense organs to the nervous system? The code is now being broken, and every evidence points to the visual system as providing the first important breakthroughs. We will soon be able to understand a great deal about the mechanisms responsible for eye movements, for convergence and divergence, and hence, for strabismus; and we can now make great inroads to the understanding at the cellular level of many of the most fundamental aspects of visual perception. Modern techniques—high-speed computers, ultrasound, and cell biochemistry—offer promising avenues to the solution of previously unresolved questions as to the nature of myopia and hyperopia and the age-old questions of the importance of environment *vs.* heredity in longitudinal variations in the degree of ametropia.

All of this and much more can reasonably be expected to be accomplished in the next few years, provided we extend sufficient support to the proper research personnel and encourage the right sort of experimental programs. We must emphasize research on cell biophysics, biochemistry, and physiology at all levels of the visual system with the latest available techniques at an increased pace. However, in our enthusiasm for research of this kind, it would be a drastic mistake if we neglected the vast amount of important experimental work that still needs to be done by psychophysical and psychophysiological methods. It was the cell physiologists' ability to build on the backlog of over 150 years of good psychophysical measurements which has brought visual physiology to its present position of preeminence. We cannot afford to allow this backlog of basic in-

formation to dwindle slowly. Psychophysical data will (and must) be relied upon indefinitely if the cell biologists' experimental questions are to continue to be insightful. Research on man and animals by psychophysical, psychophysiological, and behavioral methods must also expand if we hope to gain real understanding of the normal eye and of its various diseases.

The sequence, which begins with the first interaction of environmental stimuli with the organism at the molecular level and leads to behavioral events, has been and will continue to be most successfully studied in the visual system. The relationship between structure and functions, which has been the time-honored approach here, is certain to yield more fruitful results now that new tools of investigating structure are becoming available, and now that our capacity to localize function in the retina and the visual nervous system has made renewed progress. Within living memory we wondered at the simplicity brought to vision by the duplicity theory. Now we are at the threshold of having color vision firmly anchored in fact rather than speculation. Yet, the structural complexity of the retina remains practically unfathomed, and functions to be elucidated range from the simplest yes-no response of an experimental subject and the firing rate of a single neuron, through trigger features of ganglion and cortical cells, to ethological releasers, the recognition of patterns, and our perceptions in general.

It has become abundantly clear that major scientific breakthroughs in medical science have resulted from the research pattern so far adopted by NIH, at least in the field of fundamental physiology of the visual system. It is our recommendation, therefore, that this policy—support of the individual researcher on the basis of his past achievements and originality of his research proposal—be continued. This has been by far the cheapest and most effective way of supporting basic medical research.

One of the ultimate aims of such research is to aid in the prevention, diagnosis, and treatment of disorders of the visual system. How can the potentialities of laboratory breakthroughs be best exploited for their clinical application? The question is less urgent in connection with the heading of this chapter, "Visual Physiology," than with the other chapters of this report, which are frankly concerned with some of the more specific things that may go wrong with the visual apparatus, rather than a deeper understanding of its functioning in general. Just the same, there is a need for the laboratory scientist to be aware of the problems encountered in the clinic, and educational efforts to this end should be instituted. They may take the form of carefully written reviews to be circulated to NIH grantees and others in their class and also of symposia and conferences jointly attended by clinicians and laboratory scientists. It might be mentioned in conclusion that research is a creative endeavor that is not easy to channel in a specified direction no matter how desirable it seems. After all, is it coincidence that the word "serendipity" comes up most often in connection with research findings?

APPENDIX A

Research in this area, funded by the Visual Science Study Section in 1965, has been evaluated to determine: (*a*) The relative weight given to various aspects of this area and (*b*) who is carrying out the research. The evaluation reveals that about 7 percent of the effort is going to studies on optics of the eye and anomalies of refraction. About 9 percent is devoted to psychophysical and psychophysiological studies on retinas of patients with ocular abnormalities as well as on normal retinas. Almost 42 percent is devoted to studies of retinal characteristics, including morphology and ultrastructure of normal retina, chemistry of vision, the nature of transduction of light energy to nerve impulses, histochemistry of the retina, cell physiology, coding of the signals from the eye to the brain, electro-oculography (in man), and electroretinography (in both man and animals). Less than 2 percent is devoted to studies of the optic nerve and lateral geniculate body (all on animal eyes). Just under 15 percent is devoted to the physiology of higher visual centers, including EEG and evoked cortical potentials, the projection of the visual pathways, normal and abnormal development, lesions and visual behavior studies, and coding in the visual central nervous system. Almost 12 percent is devoted to visual psychophysics on normal man, including brightness discrimination, acuity, color vision, depth perception, time perception, and complex perceptual processes. About 9 percent is devoted to the oculomotor system, and about 2 percent to vision in invertebrate eyes.

With regard to where this research is being conducted: About 37 percent of it is carried out in departments of ophthalmology in medical schools and about one-third of that by basic scientists in those departments. Only about 5 percent is carried out in other clinical departments of medical schools, although much of the work is fundamental to these other disciplines. Seventeen percent is carried out

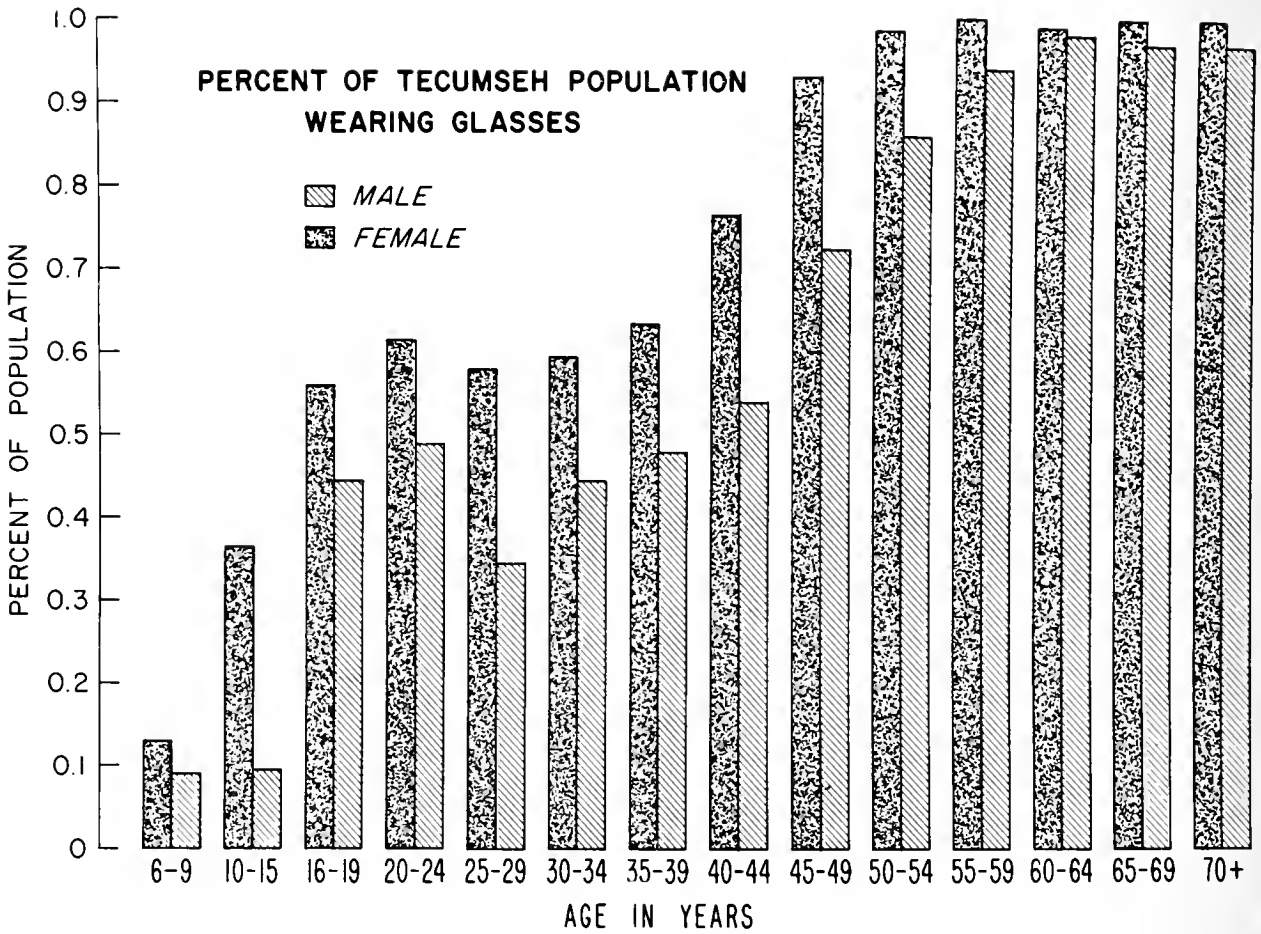

Figure 1.—The percentage of males and females in each age group of the Tecumseh project sample who wear glasses.

in basic science departments of medical schools. Almost 34 percent is carried out in university departments other than medical schools; these include psychology, zoology, biology, biophysics, chemistry, and physics. Four percent is carried out in optometry schools. The remainder (private foundations, hospitals, government and private institutes) carry out only 4 percent.

APPENDIX B*

What percentage of the normal population wears glasses? We have had the opportunity to obtain an estimate at different age levels in Tecumseh, Mich., a community of about 9,500 people. The data which follow have been made available from the Tecumseh Community Health Study (Thomas Francis, Jr., Director), which is a part of the Cardiovascular Research Center of the University of Michigan (*1*). In 1959-60, 8,641 persons—88 percent of the total population—were examined by qualified physicians from the teaching staff of the University of Michigan Medical School. Statistics of the percentage of this population wearing glasses at various ages are illustrated in figure 1. Not unexpectedly, from ages 45 (women) and 55 (men) more than 93 percent are wearing glasses. There seems to be a surprising sex difference, women showing a higher percentage at all ages. It will be seen below that this sex difference is due almost entirely to sex differences in the prevalence of myopia. In the post-puberty women, the frequency never falls below 56 percent at any age group. (It probably has never occurred to anyone that the population explosion would diminish to a frizzle if men only made passes at women who never wear glasses.)

The ages at which the adult groups started wearing glasses are illustrated in figure 2 (hyperopes) and figure 3 (myopes). The former curve is bimodal, the latter unimodal. The age at the time of examination is also plotted on these graphs in thin lines, the scale double that given in the figure. Not surprisingly, female myopes start wearing glasses earlier than

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Table 1.—*Tecumseh community health study*
[Figures in parentheses represent percent of total]

Diagnosis	Total (8,641)		Males (4,238)		Females (4,403)	
	Probable	Suspect	Probable	Suspect	Probable	Suspect
Myopia	816(9.4)	600(6.9)	287(6.8)	211(5.0)	529(12.0)	333(7.6)
Hyperopia	422(4.9)	738(8.5)	177(4.2)	268(6.3)	245(5.6)	388(8.8)
Astigmatism	468(5.4)	487(5.6)	186(4.4)	199(4.7)	282(6.4)	265(6.0)
Presbyopia	844(9.8)	484(5.6)	402(9.5)	230(5.4)	442(10.0)	238(5.4)
Strabismus	152(1.8)	114(1.3)	70(1.7)	40(0.9)	82(1.9)	68(1.5)
Blindness	150(1.7)	74(0.9)	87(2.1)	39(0.9)	63(1.4)	33(0.7)

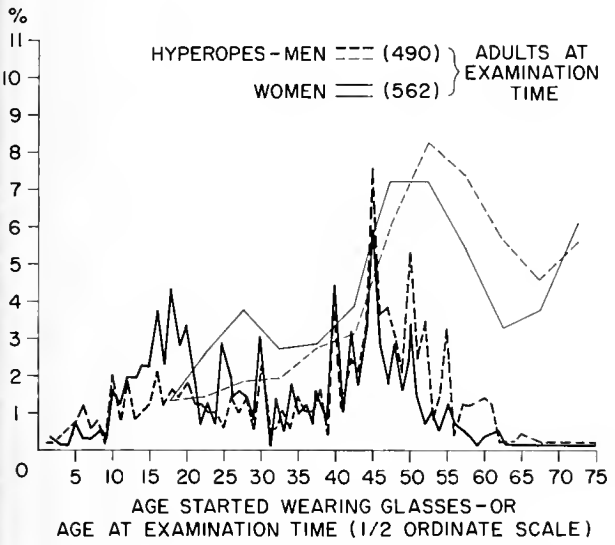

Figure 2.—The heavy lines show the age at which adult hyperopes in the Tecumseh sample started to wear glasses. The thin lines show the age at the time of examination. The ordinate scale for the thin lines should be multiplied by two.

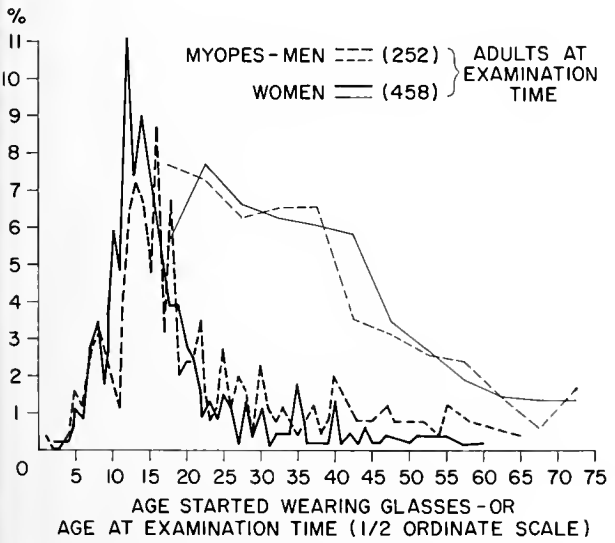

Figure 3.—The graphs are exactly the same as those in figure 2, only for myopes. Note, there are almost twice as many females as males in this sample.

male myopes. By age 30, the number of myopes who start wearing glasses is very small. Quite the opposite for hyperopes, obviously. Almost twice as many females are myopes (12 percent of the population) as are males (6.8 percent). Since there is evidence for similar sex differences among primates other than man where psychological and sociological factors are different but biological factors less so, this suggests an endocrine relation which might bear further investigation. Table I shows this sex difference in the Tecumseh project and shows that it is valid for myopia but not for the other varieties of refractive anomalies.

Only about 2.3 percent of the cases of blindness in the 1963 report of the model reporting area (*2*) were attributed to myopia. In Tecumseh, 9.4 percent of the population were listed as "probable" myopes and an additional 6.9 percent as "suspect." Assuming 2 percent of the population is blind, then only 0.3 to 0.5 percent of all myopes ever go on to blindness as a result of their myopia. Clearly, research on myopia, which might ultimately lead to a prevention or cure, will still not make appreciable inroads on prevention of blindness, but it would make life somewhat easier for a large part of the population who are forced to wear spectacle and/or contact lenses. Refractive errors may be afflictions which impose only relatively minor inconvenience on the majority of those affected, but there can be little doubt—as figure 1 clearly emphasizes—that there are few other diseases which affect such a large percentage of the population. By way of contrast, for example, only 1.8 percent of the population of Tecumseh had "probable," and 1.3 percent "suspect," strabismus. For blindness, the two figures are 1.7 and 0.9 percent, respectively, in reasonable agreement with national figures (table I).

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Chapter 5—RESEARCH IN STRABISMUS

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INTRODUCTION

Among the most highly evolved physiologic skills of man is the ability to direct and maintain the visual axes of both eyes upon an object, moving or stationary, with a resultant integrated binocular visual perception which conveys the unique property or stereopsis, or depth perception. The very real advantages of binocular single vision in a highly technological society cannot be overestimated. An elaborate anatomic and physiologic mechanism subserves the rotations of the eye yoking into an efficient binocular apparatus which greatly enhances the individual's visual performance. Motor and sensory elements contribute to this performance. Deficits in either area may disrupt the binocular mechanism, with consequent deviation of the eyes from normal binocular fixation upon the object of regard. Strabismus, the manifest evidence of such deviation, is a worldwide human ailment affecting perhaps 2 percent of the world's population.

The cosmetic blemish of "crossed eyes" is the principal factor impelling the parent to bring the affected child to the ophthalmologist. While keenly aware of the appearance of the eyes, the parent is often unaware of the attendant danger of amblyopia —the loss of vision in a habitually deviated eye. Strabismic amblyopia is a preventable disorder if caught early enough. The estimated incidence of 1–4 percent of the world's population clearly indicates the magnitude and importance of this problem.

Research in strabismus must be directed toward understanding the sensory and motor factors requisite for binocular single vision. Although certain of these factors are present at birth, the ultimate performance of the binocular visual mechanism is based upon the orderly development of skills with attendant rewards. Therefore, we must know more about the developmental processes in vision and eye movement. A comprehensive approach to the problem requires study of: (1) The oculomotor neuroanatomy and neurophysiology, both central and peripheral, including the fine structure and function of extraocular muscle; (2) the oculocerebral servo mechanisms which control the oculomotor performance; (3) the accommodative mechanism, peripheral and central; (4) the nature of fusion and its disorders; (5) neurogenic, transmissional, and myopathic disorders of ocular motility; and (6) the development and aging of the sensory and motor components of the oculomotor system.

ANATOMY AND PHYSIOLOGY OF THE OCULOMOTOR SYSTEM

Neurology

1. *Supranuclear mechanisms.*—A vital area of research is concerned with the neurophysiology of cortical control mechanisms. Stimulation experiments coupled with anatomic studies of primates and man, such as those performed by Crosby and her associates (*35, 36*), must be carried out with even more sophisticated techniques. The use of microelectrode recordings of cortical cells or areas correlated with ocular rotations is an example. There appears to be a broad representation in oculomotor function throughout the cortex, and stimulation studies have demonstrated virtually all types of eye movement. Whether true cortical centers for ocular rotations exist is in dispute (*91*). The interrelated facilitation and inhibition of motor activity has been investigated (*54, 93*). The results indicate that an extremely complex system governs the various types of eye movement. It was shown that both versions and vergences may be controlled by cortical "centers." The three components of the near reflex in the macaque—accommodation, convergence, and miosis, have been elicited by stimulation of areas 19 and 22 in the preoccipital cortex (*60*). Conjugate and disjugate movements have been shown to be independently controlled (*95*). The central control of vergence is suggested by the influence of alcohol, sedatives, stimulants, anesthesia, and sleep (*17, 116*).

2. *Nuclear Centers and Mechanisms.*—The concept of a midbrain center for convergence in the nucleus of Perlia has been dispelled (*113*). The components of the oculomotor nuclei have recently been

mapped by stimulating branches of the oculomotor nerve (*102*). The accommodative response has been isolated through midbrain stimulation in the monkey (*57, 60*). Using the technique of retrograde chromatolysis, Warwick (*112*) has shown the arrangement of the nuclear centers for the extraocular muscles to be different from that pictured by electrostimulation techniques (*10*). These conflicting results show the need for continued investigation.

Neuromuscular Junction

Intensive research must be done on the ultrastructure, histochemistry, and electrophysiology of the myoneural junction if we are to elucidate the nature of synaptic transmission. Myasthenia gravis has been much studied because the defect is believed to lie in the neuromuscular junction complex. Recent investigations implicate the presynaptic area as the locus of disturbance (*38, 40*). An autoimmune mechanism, in which antibodies are produced against myoneural junction, is receiving much attention at the present time (*102a*). The association of thymus hyperplasia and tumors with myasthenia is most suggestive of such a mechanism. Disturbances in the myasthenic neuromuscular junction have been reported with histochemical (*125*) and electron microscopic techniques (*128*).

Myology

Extremely important and exciting work is being done on the ultrastructure and physiologic characteristics of extraocular muscle, following the early work of Kruger (*66*) and the significant papers of Hess and Pilar (*53*), who demonstrated the presence of slow and fast fiber systems in this muscle. Observations on these fibers have been amplified by Dietert (*41*), Kern (*65*), Cheng and Breinin (*28*), and Matyushken (*80a*).

The slow fiber of extraocular muscle (*felderstruktur, afibrillar*) shows large, irregular, poorly defined fibrils with multiple motor endings of the *en grappe* type all along its length. These fibers contain clumps and bundles of myofibrils which are very poorly delimited by sarcoplasmic reticulum. Abundant mitochondria are present within the fibers. The Z band is often wavy, and the M band is faint or absent. The transverse tubular system is absent or vestigial. The slow fiber shows an intense reaction with nitro blue tetrazolium, indicating an active succinic dehydrogenase mechanism. This enzyme activity is longitudinally distributed in the fiber. *Felderstruktur* fibers are smaller in diameter than the fast-twitch (*fibrillenstruktur, fibrillar*) fibers. The twitch fiber contains one or, at times, two motor end plates (*en plaque* endings), usually located at the junction of the proximal and middle thirds. This fast fiber contains myofibrils that are grouped in well-demarcated bundles abundantly surrounded by sarcoplasmic reticulum. There is a sparse scattering of mitochondria, and the fiber stains lightly with nitro blue tetrazolium. There is a strong Z band and well-defined M band and transverse tubular system. High magnification of both types of fibers shows fine and coarse myofilaments measuring down to 50 angstroms. Both grapelike and plaque nerve endings stain well with cholinesterase stains (acetylthiocholine method), indicating a cholinergic motor function for both (*27a, 124*). An ultrastructural study of the nerve endings shows that the *fibrillenstruktur* fiber has typical junctional folds with a clearly demarcated basement membrane. Abundant synaptic vesicles containing acetylcholine are present in the nerve ending. In the *felderstruktur* nerve ending, there are few and rudimentary junctional folds. Synaptic vesicles containing acetylcholine and a few larger granular vesicles (possibly containing catecholamines) are present, suggesting adrenergic as well as cholinergic function. A twitch fiber showing intermediate characteristics has also been observed (*28*).

The two main fiber types of extraocular muscle also exhibit distinct electrophysiologic properties. The twitch fibers show propagated, all-or-none action potentials and fast, twitch-type contractions. The slow fibers demonstrate only small junctional potentials and graded contractions (*53, 80a*). In these characteristics, the two fiber types appear entirely similar to those that have been described in the peripheral skeletal muscle of the frog by Kuffler and Vaughn Williams (*67, 68*) and by Peachey and Huxley (*92*). An early suggestion (*2*) that the thick and thin fibers of extraocular muscle subserve versions and vergences respectively, the former being somatic and the latter autonomic in function, has received some support because of the demonstration of the two fiber types. However, the implication that the slow fiber is responsible for the vergence—slow, tonic movement—and the fast fiber for the version phasic, or saccadic, movement, while intriguing, has no experimental confirmation at the present time. A differential pharmacologic sensitivity of the two systems is evident (*vide infra*). This is clearly an area of great theoretic and clinical importance, and intensive investigation must be carried out on the structure and function of the different fibers with an aim to determining what, if any, clinical correlations exist and whether certain aspects of comitant and incomitant strabismus and possibly nystagmus are related to the fiber types.

Very little is known of the aging process in extraocular muscle. It has been suggested that senescent morphologic alterations which resemble myopathy occur in this tissue (*82*). A systematic study of such changes in primates and man should be carried out.

Innervation of Muscle

Very little is known about the innervation of extraocular muscle (*69*). Studies on the motor-unit-control mechanism such as have been carried out in skeletal muscle (*22*) involving analysis of the anatomical and electrical motor unit, the rhythmicity of firing patterns and periodicities, and the relationship—if any—to a biological clock remain to be carried out in depth. Computer techniques will prove essential in these determinations. It is conceivable that such theoretic material could produce significant insights into clinical problems (*58*).

Of fundamental interest is the constant tonic activity of extraocular muscle in the conscious state. The factors maintaining this activity are still conjectural but appear to implicate the reticular arousal mechanism and possibly proprioceptive end organs. Depression or inhibition of this activity characterize anesthesia and sleep (*17*). In recent studies, an amnesic but conscious stage during the induction of general anesthesia was attended by electrical silence of the extraocular muscles (*15*). In a study of succinylcholine effects, the extraocular muscle activity varied, as did the tidal volume of air maintained by diaphragmatic respiration. This similarity in behavior of extraocular and diaphragmatic muscle is of interest with respect to their involvement in myasthenia gravis (*15*).

Kinesiologic studies of ocular motility have demonstrated a general law of innervation which states that the innervation parallels the position of the eye (*20, 85*). The extent to which slow-fiber muscle activity, which is not electrically recordable, may influence ocular motility is presently unknown but constitutes a new and critical point of departure in such studies.

Physiology and Pharmacology of Extraocular Muscle

The physiologic and pharmacologic characteristics of extraocular muscle have been recently reviewed (*16*). The pharmacologic responses of extraocular muscle essentially parallel those of peripheral skeletal muscle. The quantitative distinctions that have been described may indeed relate to the differential sensitivities of the two fiber systems. The differences between extraocular and peripheral skeletal muscle reported in the literature have been explained as largely due to differences in experimental techniques. When stimulating drugs are given by close arterial injection, the sensitivities of extraocular and peripheral skeletal muscle approximate each other. The fact that succinylcholine elicits a contracture (nonelectrical contraction) of extraocular muscle may relate to its ability to differentially affect the *felderstruktur* fiber while causing a complete depolarization of the *fibrillenstruktur* fiber. If succinylcholine acts through a beta adrenergic receptor mechanism, the possibility must be investigated whether beta adrenergic inhibitors can, in fact, lyse such action.

Recent studies have shown a surprising and previously unrecognized sensitivity of extraocular muscle to norepinephrine, the muscle undergoing a slow, tonic contraction (*43, 44, 58*).

A study of the length-tension curves of extraocular muscle showed a basic similarity to those of peripheral skeletal muscle; no evidence of an autonomic muscle component was obtained (*16*).

OCULOMOTOR MECHANICS

Research in this area, although most important, remains in short supply. There has been much speculation but little definitive investigation on the action of muscles (*105*). Of current interest are the transposition and stimulation experiments of Bloomgarden and Jampel (*14*), which suggest variability and adaptability in function of specific muscles. They showed that conjugate rotations were regained following transplantation of extraocular muscles in the monkey and that neither vision nor fusion were factors in this recovery. The function of individual extraocular muscles was also demonstrated by selective stimulation of the oculomotor nerves (*61*). They failed to find evidence of a fixed center of rotation. These studies must be expanded in primates and the relevance to man established. The results may be of particular significance in the surgical management of strabismus.

NEUROPHYSIOLOGY OF OCULOMOTOR SYSTEM

Measurement of Eye Movement

Various techniques have been devised to study eye movement. Optical methods based on corneal or retinal reflections have been utilized. Contact-lens mirrors have been affixed to the globe, and the reflection recorded on photographic paper or by photomultiplier tubes and then displayed on oscilloscopes. These techniques have a high degree of sensitivity. Electro-oculography is a technique which records the variation with eye movement of a standing corneoretinal potential. It is subject to many sources of error but is widely employed for clinical testing. More recently (*117*), electromagnetic records of eye movement have been obtained with high sensitivity (*10*).

An ingenious marker camera, designed by Mackworth and Llewellyn Thomas (*78*), photographically

records the ocular movement in relation to the target. It permits recording ocular fixations on objects of interest and also has been used to show kinetics of eye movement (*70*).

Further studies on methods showing good reliability and high sensitivity for recording eye movement are needed.

Oculomotor Servomechanisms

In addition to extrafusal fibers, intrafusal or spindle fibers are also present in extraocular muscle. They have been extensively studied by Cooper, Daniel, and Whitteridge (*32, 33*). Whitteridge (*119*) demonstrated a gamma efferent system innervating the intrafusal fiber of extraocular muscle, thus showing that it is under central neural control. The intrafusal fiber nerve endings also take cholinesterase strains, indicating the cholinergic function of the gamma efferent system. The role of such proprioceptive end organs is, however, completely unclear. Proprioception from extraocular muscle has long been shown not to relate to position sense. That some spindle function exists, however, is indicated by the fact that stretch of the intrafusal fibers does trigger impulses ascending through the motor nerves of the extraocular muscles into the central nervous system. Typical A and B spindle discharge patterns have been recorded (*33*). It has been suggested that such proprioceptive inflow may concern the constant tonic activity of extraocular muscle which is so peculiarly characteristic of the waking state (*20*). This constant activity appears to be related to activity of the reticular arousal mechanisms and can be shown to disappear during deep anesthesia and deep sleep. The possibility also exists that the proprioceptive mechanism is essentially outflow in type (*120*). According to the outflow theory, we have knowledge of the flow of motor impulses to the eye muscles, whereas by the inflow theory, the central nervous system is informed of peripheral events by the afferent impulses arising from proprioceptors of the eye muscles. Ocular muscle proprioceptors do not play any significant part in conscious appreciation of eye movement and do not seem to be responsible for any form of stretch reflex. They may modify adversive movements initiated by retinal stimuli and may play a role in maintaining fixation (*30, 120*).

Model servo systems must be developed through application of physiologic and engineering principles. A number of such systems have been adumbrated, utilizing computer methodology, with respect to pursuit, saccadic, and vergence movements (*31, 39, 47, 127*).

Sensory Control of Eye Movement

Very little is as yet known about the psycho-optical reflexes for fixation and fusion. The fundamental importance of these reflexes for binocular vision is well established. Fixational reflexes are primarily concerned with versions, which have been shown to be capable of great speeds (400° to 600° per second). It is interesting that, while voluntary attention is necessary for a saccade to occur in response to a fixation target, the velocity is independent of voluntary control or practice (*117*) (Westheimer; Hyde) (*55a*). Fusional reflexes are primarily concerned with vergences in the interest of binocular vision and are characteristically slow (10° to 20° per second). The stimulus for fusional vergences is retinal disparity of the image. The completed response, in effect, reduces the disparity to zero. However, the way in which the stimulus evokes a response and just how fusion is maintained following the movement are still very much unknown. Studies in this area strike at a fundamental problem in strabismus. Is fusion innate, or can it be trained? What is the relationship of Panum's area to fusion? The stereopsis that occurs with fusion needs to be investigated, since the sense of depth can occur without fusion (*89*) and in the presence of fixation disparity. Important information was obtained by studying the characteristics of fixational and fusional reflexes together (*126*). Such work has led to the concept that these two kinds of movement are subserved by separate mechanisms.

Clinical applications in the area of binocular vision are widely employed in orthoptics on an empirical basis, but with little or no physiologic insight. The neurophysiologic meaning of correspondence is still very unclear, as are therapeutic approaches to abnormal correspondence. The unresolved problem of correspondence remains central to strabismus, since a functional cure is predicted upon normal correspondence. The nature of fixation disparity has not yet been fully adduced (*3*), nor is its relation to small-angle esotropia clear. The whole concept of the adaptive modifications of the sensorium in strabismus requires critical evaluation.

The sensory performance of the eyes constitutes a prime area for interaction of the various disciplines concerned with vision. Cooperative investigations by physiological psychologists, physiologists, and ophthalmologists have led to rewarding discoveries. The need for training programs to develop more such personnel in this area is clear. Every ophthalmological training program should include one or more visual physiologists.

Accommodation

1. *Sensory factors.*—It has been generally assumed that the stimulus to accommodation is a blurred retinal image. However, blurred images may be produced by foci in front of or behind the retina. What, then, is the nature of the stimulus that evokes the proper accommodative response? Fincham suggested

that chromatic aberration and the directional sensitivity of retinal receptors to light vergence (Stiles-Crawford effect) are important (*48*). It has been proposed that oscillations in accommodation play an important role in determining the direction of the accommodative response (*4, 26*). Quite significant in these studies is the understanding of the depth of focus in which the accommodative response lags behind or overshoots the stimulus while clear vision is still maintained (*27*). Little is known about the proximal stimulus (awareness of nearness) to accommodation. Early studies showed that there was proximal convergence but no proximal accommodation (*55*). This idea should be challenged, because the normal accommodative stimulus may prevent occurrence of proximal accommodation. Since the exact nature of the stimulus for focusing is not known, it would be difficult to dissociate it from the fixation situation in which there is a proximal factor. New types of controlled experimental situations will be required to solve this problem.

2. *Motor factors.*—While the influence of the parasympathetic nervous system on accommodation is accepted, much needs to be learned about sympathetic influences. Early studies showed the latter reduced the refractive state of the eye (*86*). Just what effect the interplay of the two systems has on the normal increase and decrease in accommodation requires sophisticated pharmacologic and time-course studies of the accommodative response.

The peripheral accommodative mechanism is an intriguing area which involves ciliary muscle physiology, muscle-lens linkages, and the physical properties of the crystalline lens. Recent studies have shown the ciliary muscle to be intermediate in type between the autonomic and somatic systems (*59, 97*). The significance of this must be interpreted in light of the "synkinesis" between accommodation and convergence. Recently Weale (*114*) has suggested that presbyopia need not result from sclerosis or hardening of the lens substance. He proposed that recession of the near point may be caused by a shift in the balance of the respective opposing elastic forces of the capsule and the lens substance. This is brought about by the continued growth of the lens substance, which tends also to reduce ciliary muscle effectiveness by approximation of the lens equator to the ciliary body.

3. *The linkage between accommodation and convergence.*—When accommodation is stimulated, convergence responds by reflex. It is believed, therefore, that there must be a central synkinesis or linkage between the two functions. The apparent linearity of the ratio between the two responses suggests that the central innervational ratios may also be linear. This concept forms the working hypothesis on which we explain many of our clinical findings (*5, 79*). There is great need to verify this hypothesis by electrophysiologic and pharmacologic techniques, coupled with histological studies of stimulus areas in the cortex, midbrain, ciliary ganglion, and ciliary muscle (*60, 100*). In addition, our understanding of this synkinesis may be enhanced by clarifying differences between the response AC/A and stimulus AC/A ratios in psychophysical experiments and correlating these with the depth-of-focus factor (*5, 98*). There is also a need to emphasize and study the reverse relationship; that is, a stimulus to convergence can also elicit accommodation. The methods for studying this relationship are more difficult, but quite necessary for expanding our knowledge of the fundamental relationship between these functions. The experimental difficulty lies in the elimination of the accommodative stimulus while still maintaining fusion (*49*).

The accommodative convergence relationship is most important in our management of accommodative strabismus. It is known that, in addition to hyperopia, a high AC/A ratio contributes significantly to this type of esotropia. Why, then, do some patients have high ratios? Is is that they have a basically high central innervational relationship between these two functions, or is it primarily due to excessive effort to bring about a given accommodative response? The answers to these questions require careful studies on the effect of drugs and age on the AC/A ratio and the amplitude of accommodative response. Proximal effects on accommodation and convergence must be clarified in order to determine precisely the effects of the synkinesis on the near esotropia. Both convex lenses and anticholinesterase miotics have been used to treat accommodative esotropia. The miotics, by potentiating the transmission across the ciliary neuromuscular junction, reduce the central effort necessary for accommodation, which is reflected in a reduced accommodative convergence (*100*). The discovery that miosis per se is not important in the therapeutic response has led to the use of a mydriatic-miotic combination for effective prevention of miotic-induced iris cysts (*29, 98*). It should be pointed out that recent studies show that, with miotics, patients continue to make the normal accommodative responses with reduced accommodative convergence. On the other hand, convex lenses inhibit such responses. The long-term relative value of the two methods of management needs to be determined (*18*). The use of experimental animals and various drugs which can influence accommodation in different ways and at different levels must be supported by further research. Such studies may ultimately lead to a much more effective medical control of accommodative vergence, which will prove of major significance in the treatment of accommodative strabismus.

HETEROPHORIA AND COMITANT STRABISMUS

Very little is as yet known about the etiology of strabismus. Being a disjunctive change from the binocular position of the eyes, the defect has been ascribed to an anomaly of vergence (*1*). It has also been considered an anomaly of version and has been attributed to delective myelination (*64*). The central origin of the anomaly is suggested by the influence on the fusion-free position of various centrally acting drugs, such as amphetamine, barbiturates, and alcohol (*116*), as well as of sleep and anesthesia (*17*). Added to our need to understand comitant strabismus as a vergence anomaly is the question of how fusional ability may or may not compensate for the defect. This relates to the concept of heterophoria, its causes, and how it develops into heterotropia. The influence of supranuclear factors is poorly understood. The plenitude of terms which mean different things to different people is a hindrance to furthering our understanding of the nature of comitant strabismus. For example, the term "divergence" may mean, to some, disjunctive movement from the fusion-free position at distance. To others, divergence starts from the parallel alignment of the eyes. The significance of the "center" concept depends on which definition one holds. The breakdown of vergence into tonic, proximal, accommodative, and fusional components requires scientific amplification and clarification (*50*).

Medical Therapy

The use of drugs should be studied with reference to their effect on the angle of strabismus. This is an exciting area in which only a beginning has been made. The finding of two types of nerve and muscle fibers which may subserve two different ocular functions is encouraging (*53*). This may permit a new pharmacologic approach to strabismus. So far, only anticholinesterase agents for the treatment of accommodative esotropia have achieved a secure place. Recent demonstrations of the cataractogenic action of the long-acting anticholinesterases may force a reassessment of their use in patients. This effect has not yet been shown in children, but it points up the need for a continuing search for nontoxic agents to control accommodation. Agents acting upon the central nervous system should be systematically explored.

The role of glasses for the accommodative factor is well established, but the combination of glasses and miotics may provide far better control of this type of strabismus; however, they play a limited role, particularly for the incomitant types and for small residual deviations. The role of orthoptics, in use throughout the world, remains controversial. A statistical study of its accomplishments is required.

Surgery is usually the only way to effect a permanent change in the angle of nonaccommodative strabismus, but it plays a very small role in accommodative strabismus. Various influences on comitant strabismus should be further investigated—for example, the effect of vertical incomitancy on the angle of strabismus such as occurs in the A-V syndromes, refractive errors, anisometropia, and aniseikonia. The existence of periodically recurring strabismus suggests a biological-clock mechanism which may yield therapeutic clues.

Surgical Therapy

The role of surgery in nonaccommodative strabismus is clearly established. To an ever-increasing extent, however, surgery is taking a back seat to the advancements in medical science. As new areas of medical therapy develop, the number of surgical indications diminishes. Thus, accommodative strabismus is clearly outside the surgical realm, except in a few instances of abnormal AC/A ratios, where a large angle deviation is present at near that cannot be suitably handled by other means. For the nonaccommodative element, tonic, structural, or mechanical deviations, surgery remains the only practical therapy. It has long been evident that purely mechanical concepts of surgery are inadequate, since it is impossible to reduce the procedure to a simple formula of millimeters of surgery per diopter of deviation. Although clinical rules have been established which purport to do this, the method is basically of little merit. Multiple factors affect the surgical decision and result. Research in surgery involves continuing studies of large series of patients treated by different techniques in which standard methods of measurement have been utilized. It is a difficult problem to equate one man's surgery with another's, and failure to standardize methods of diagnosis, as well as surgical techniques, has led to chaos. It is impossible to equate all the sensorial and motor factors of a given case with those of any other case, but a standardized approach in large series will allow fruitful comparisons. Efforts by international societies to establish such common denominators in diagnosis and therapy should be encouraged, so that the results of any group of investigators will be relevant to all work in the field. Standardization, therefore, must be considered a primary requirement in the field of ocular muscle surgery.

Improvement in surgical techniques requires experimental studies in primates and, ultimately, application to man. Studies in ocular muscle kinesiology and mechanics should be encouraged, since they will lead to a greater appreciation of the function

and surgical role of the muscles. It is particularly important to achieve a better understanding of the anatomy of the vertical muscles and of their surgical indications and approaches.

Improvements in suture materials and instrumentation will always be necessary. Among the problems to be resolved are the occurrence of granulomas and cysts, and the prevention or mitigation of scarring, which may vitiate the results of both the original and any subsequent surgery.

INCOMITANT STRABISMUS

Incomitant strabismus may result from a host of etiologic factors involving neurogenic, junctional, and myogenic disorders. Disturbances may occur at the supranuclear, nuclear, and infranuclear levels. Motility disorders constitute a large part of the subject matter of neuro-ophthalmology. Research in this area involves the full spectrum of the neural sciences, with participation by neurologists, neurosurgeons, ophthalmologists, otologists, neurophysiologists, neuroanatomists, neurochemists, and other basic scientists. The pooled talents of this group offer the best hope of achieving significant progress in neuro-ophthalmologic disorders.

A fundamental problem of incomitant squint is the nature of the paretic process and how it produces paretic strabismus. In a review of this subject, (*20*) Breinin suggested that loss of innervation of the antagonist does not per se cause paretic strabismus, but that the antagonist undergoes an increase of activity which pulls the globe into its field. Ultimately, the uninhibited action of the antagonist results in clinical contracture, which produces comitancy and prevents restoration of binocularity even when the originally paretic muscle recovers. The possible role of the slow muscle fiber in the paretic process is a fascinating subject for investigation.

The nature of reciprocal innervation and reciprocal inhibition is still not well known, and the clinical entities which provide insight into these processes must be carefully studied.

Internuclear ophthalmoplegia is an example wherein dissociation of reciprocal innervation and inhibition, and a brain-stem tonicity mechanism as well, have been demonstrated by means of electromyography (*20, 96*).

Careful analytic studies of clinical material will add greatly to our understanding of physiologic processes and their aberrations in disease.

The technique of extraocular muscle electromyography has had its chief clinical use in the field of paretic disorders (*12, 20*). It has proved valuable in Duane's retraction syndrome, the Brown sheath syndrome, and various structural disorders, such as blow-out fracture of the orbit. The concept of anomalous innervation, which is of great theoretical interest, has not been satisfactorily explained (*13, 19*).

AMBLYOPIA

Amblyopia may be defined as a loss of vision which is without visible cause and which is not correctable with lenses. Strabismic amblyopia, the most important type, results from suppression of vision in a habitually deviated eye. It is sometimes referred to as suppression amblyopia. Another type is associated with anisometropia, or unequal refractive error, the more highly ametropic eye experiencing the loss of acuity. Hence it is also called amblyopia ex anopsia, or disuse amblyopia, due to the failure to achieve a useful visual image.

It is possible that in some cases organic pathology such as the sequellae of macular hemorrhage in the newborn may underlie an amblyopia, but surely such an etiology must be uncommon. Although it is commonly believed that strabismic amblyopia is a functional disorder, reversible within limits, current animal research points to the possibility of organic pathology resulting from very early disturbance of the binocular visual mechanism. Such pathology may occur at higher levels than in the retina —for example, in the lateral geniculate body or visual cortex (*121, 122, 123*).

The incidence of amblyopia varies in different reports, but estimates ranging from 1 to 4 percent have been proposed. On this basis, as many as 7 million Americans may be affected. This constitutes a public health problem of major proportions. Of particular significance is the fact that amblyopia is a preventable disorder, provided adequate diagnosis is established in early childhood. It is generally accepted that by the age of seven or eight the visual mechanism achieves adult fixity; thus amblyopia which can be successfully treated prior to that age is no longer readily reversible later. The recently introduced techniques of pleoptics have had a limited success in coping with the problem of amblyopia in both children and adults. For amblyopia, prevention is still of the essence.

The past 15 years have witnessed remarkable developments in the theory and therapy of strabismic amblyopia. Bangerter (*8, 9*) and Cuppers (*37*) have radically altered traditional therapeutic approaches to the problem and have given new impetus to research directed toward elucidating the physiopathological bases of amblyopia.

Several questions have not yet been definitely answered. (1) Is strabismic amblyopia primarily a sensory or a motor disorder? (2) Is the locus of the disturbance in strabismic amblyopia retinal, cortical, or a combination of both? (3) Is eccentric fixa-

tion an essential aspect of amblyopia? (4) Is the essence of eccentric fixation a decrease in visual acuity associated with fixation shift to a point at the margin of the central scotoma, where resolution is better? (5) Is a shift in visual direction the chief feature of the eccentric point? (6) Is there a shift of the zero point of retinomotor value from the fovea to the eccentric element?

The natural history of amblyopia involves the phenomena of retinal rivalry, ocular dominance, and facultative and obligatory suppression. Very little is known about these psychophysical elements and their exact role in the progression toward amblyopia. It is, however, clear that there is a temporal sequence in the development of amblyopia, so that an opportunity is available to analyze the predisposing factors. Here is a fruitful area for research in physiological psychology.

Central to a discussion of amblyopia is the study of normal visual acuity. There is a very sharp gradient of acuity at the fovea, which decreases rapidly but regularly and smoothly in all directions from the fixation axis without breaks at the anatomical zones of the macula. Studies by various investigators showed differing results. At the edge of the macula, which is about 2.5°, acuity is 0.5; at 7.5°, the acuity is 0.25; and in the periphery of the retina, acuity is about one-fortieth that of the fovea, according to Wertheim (*115*), whose studies did not extend closer than 2.5° of fixation. Weymouth (*118*) examined the central 2.5° of fixation. At 21 minutes from fixation, the acuity was 0.8. The technique of Jones and Higgins (*62*), who examined the area within 1° of fixation, showed that there was a marked falling off in visual acuity at 10 minutes from the fovea (V.A.= 0.75). A 5 percent drop occurred at 3.5 minutes from the fovea. They concluded that there is only a small region of retina, 7 minutes of arc in diameter, within which highest visual acuity is obtained. They agreed with Weymouth that the sharp acuity gradient is the basis of fixation. The accuracy of fixation is about 2.5 minutes, and they considered that physiologic nystagmus acts as a corrective process. Slight eccentricity of fixation, therefore, can produce a marked decrease in visual acuity, and such slight eccentricity might be clinically unrecognizable.

Research in amblyopia has been intensified in recent years. Harms (*51*) reported an altered pupillomotor value of light stimulation in the amblyopic eye. In normal eyes, the pupillary reaction was much brisker with central-zone stimulation than with peripheral stimulation. In amblyopic eyes, on the other hand, the central sensitivity was relatively less. He concluded that the defect in strabismic amblyopia must be located below the geniculate body, and that it must lie in the retina. He felt that the inhibitory process, while originating in the cerebral cortex, was projected centrifugally so as to suppress the activity of the retina itself.

Wald and Burian (*111*) believed that the inhibition Harms described could operate at the cortical level upon a hypothetical pupillomotor center. Their studies showed that the absolute light threshold, dark adaptation, and spectral sensitivity to various wave lengths, centrally and peripherally, were normal in the amblyopic eye. The entire apparatus of light and color perception and spatial localization, therefore, appeared normal. Hence, they attributed the impaired acuity of the amblyopic eye to inhibition of the higher cortical function of pattern or form vision without impairment of a lower cortical function of light perception and spatial projection. It has been shown, however, that the light threshold is elevated in the amblyopic eye (*75*).

Wald and Burian also pointed out that an animal whose occipital cortex is removed loses all capacity for pattern vision, while retaining sensitivity to light and brightness. As will be seen, the question of whether the locus of the disturbance in amblyopia is cortical or retinal has never been satisfactorily answered.

Evidence in favor of a cortical locus was presented by Dyer and Bierman (*42*), who reported abnormal, spontaneous cortical potentials in suppression amblyopia. Burian and Watson (*23*) demonstrated that the electroencephalogram of some amblyopes differed from the normal in certain respects. Stimulation of the amblyopic eye by repetitive light stimulation inadequately suppressed the alpha rhythm, while stimulation of the normal eye suppressed the alpha rhythm effectively. Photic driving was normal when the good eye was stimulated, but was abnormal when the amblyopic eye was stimulated. It cannot be stated, however, that these data rule out a retinal locus.

Other studies of the EEG have also shown certain abnormalities in the amblyopic individual (*34*).

Van Balen and Henkes (*106*) concluded, on the basis of waves representing the foveal and the nonfoveal mechanisms, that the electroencephalographic response from the amblyopic eye resembles that of the normal eye without visual attention. They believe visual attention is mediated by the reticular formation through centrifugal fibers to the retina.

In a study of photic driving, it was reported that the only difference between normal and amblyopic eyes occurred when the subjects had both eyes open (*83*).

Although the electroretinogram with single flashes or flicker has been reported as normal in amblyopes by Keiner (*64*), Karpe (*63*), Nawratzki and coworkers (*87*), and Burian and Lawhill (*24*), this observation has no real significance, since the ERG is a mass effect. With refined techniques, however, it

should be possible to test macula function alone. Even computer studies of the ERG in amblyopia under carefully controlled conditions failed to demonstrate a difference (*24*).

In a study of the ERG and evoked occipital response to photic stimulation, no significant differences were found in the ERG, but there was a significant prolongation of the latency of the primary response in the evoked occipital potential of the amblyopic eye as contrasted with normal values in the good eye (*87*). This lengthening of latency of the evoked response agrees with the prolongation of perception or reaction time in the amblyopic eye (*72, 107*).

The technique of critical flicker frequency has been used to study retinal function. This property is thought to reside within the retina. The normal CFF record shows a difference between the center and the periphery. Some studies indicate a higher central than peripheral CFF, and others the reverse, depending upon the techniques employed. All studies have shown that there is a disturbance of CFF in the amblyopic eye, so that the central and peripheral values approximate one another, the normal differential being lost. Teraskeli (*104*) found the CFF to be higher in the periphery in normal eyes, with this difference disappearing in the amblyopic eye, partly by an increase of central CFF, and partly by a decrease of peripheral CFF. Miles (*81*) had somewhat similar results. Feinberg (*46*) reported higher central CFF over the periphery in normal individuals, but in amblyopes, he found that the central CFF was depressed. This depression of CFF paralleling the depression in visual acuity is evidence, according to Feinberg, that form vision and primitive light mechanisms are not dissociated in amblyopia, and that the retina is involved.

Ludvigh (*71*) demonstrated with small angle visual stimuli that the foveal light-difference sensitivity of the amblyopic eye is less than that of the normal eye. He also showed that brightness discrimination in amblyopic eyes is markedly lower than in normal ones. This was also reported by Miller (*83*), but Irvine (*56*) found less marked differences. Ludvigh proposed the hypothesis that on-off elements mediate binocular fixation, contour perception, and visual acuity, and that these elements or their neural output are suppressed in the initial stages of amblyopia ex anopsia.

Pugh's studies on amblyopic eyes (*94*) suggested that cortical inhibition was responsible in about 50 percent of the cases, since the acuity of some amblyopic eyes decreased further when the good eye was open.

In more recent studies, Pugh (*94a*) suggested that a disturbance of the foveal receptors and pigment epithelium was responsible for deep amblyopia.

Mackensen (*73, 74*) showed the light threshold of the eccentric fixation area was even higher than that of the scotomatous macula, increasing further with binocular fixation.

A major problem of amblyopia centers around the question of fixation. Numbers of studies have demonstrated that, although central fixation does occur, it is uncommon in the higher degrees of amblyopia, and that minor degrees of eccentric fixation are extremely common, in fact, are the rule, even in the lesser grades of amblyopia. A number of fixation tests have been described, such as the Brock and Givner test (*21*), which purports to show that projection of an amblyopic eye is eccentric in all but about 20 percent of amblyopes. This technique has been criticized as demonstrating binocular projection function rather than monocular eccentric fixation. Hauser and Burian (*52*) showed that the eccentricity demonstrated by the test corresponded to the angle of anomaly; further, that a strong central stimulus could elicit central fixation. Nevertheless, many of these eyes did demonstrate eccentric fixation with casual stimulation.

Mackensen (*75, 76, 77*) reported upon the fixation patterns of the amblyopic eye and upon the characteristics of saccadic movement in such eyes, using the technique of electro-oculography. He demonstrated marked instability of fixation movement by the amblyopic eye as compared with the smooth fixation of the normal eye. These findings were confirmed by von Noorden and Burian (*108a*), and by Mackensen (*109*), who also demonstrated the unsteady fixation and irregular saccadic movement of an amblyopic eye as contrasted with the steady fixation and regular saccadic movement of the normal eye. These authors further demonstrated that, under conditions of dark illumination, the amblyopic eye performed exactly as did the normal eye. Von Noorden and Burian (*108*) also confirmed Ammann's (*6*) observation that the amblyopic eye responded differently to neutral density filters than did the normal eye. Thus, a normal eye experienced a decreased visual acuity behind a sufficiently dense neutral density filter. The amblyopic eye, on the other hand, either had no reduction in visual acuity, retained the same level of acuity, or actually improved in acuity. With organic lesions of the macular area, however, there was a marked loss of visual acuity when the neutral density filter was interposed.

The investigators thus distinguished between organic amblyopia and suppression amblyopia. The study of visual acuity under varying illumination (*108*) also demonstrated that the amblyopic eye actually improved in acuity with diminishing illumination, even equalling the normal eye, whereas the normal eye decreased in acuity with diminishing illumination. Studies by von Noorden and Burian

(*108a*) which showed the marked improvement of fixation and acuity of an amblyopic eye in dark adaptation or during intermediate levels of illumination (termed "mesopic"), support their thesis that amblyopia is a function of the cone system, operative during photopic illumination.

A new concept, receptor amblyopia, has been described by Enoch (*45*). Utilizing an experimental evaluation of the Stiles-Crawford effect (the observation that the luminosity of rays axially directed toward the foveal cones is greater than that of rays obliquely directed), he found that a number of amblyopes exhibited malorientation of their foveal cones. This surprising observation indicated an organic element in some amblyopes for which no mechanism is currently known. More experimental work is required to properly evaluate this finding.

Von Noorden and Mackensen (*110*) employed fixation photography and electro-oculography to find support for Cuppers' correspondence theory, which predicates eccentric fixation upon anomalous correspondence. Later, however, von Noorden (*107a*) studied fixation in twenty patients, making the following point: the relationship between anomalous retinal correspondence, the angle of deviation, and the fixation behavior indicated that the correspondence theory of Cuppers and his definition of eccentric fixation may apply only in a limited number of patients—those in whom the postulated close relationship between these factors can be found. In the majority of his patients, however, no such close relationship was found. Eccentric viewing (looking past rather than directly at the test object) rather than eccentric fixation was encountered, suggesting that the patient utilized a retinal area possessing a relatively higher resolving power under monocular conditions.

Oppel (*90*) disputed Cuppers' correspondence theory and proposed the "preponderance theory," stating that a patient may fixate with the center of a suppression scotoma if that area has the highest visual acuity.

Stuart and Burian (*103*) preferred the term "crowding difficulty" to "separation difficulty" (the inability to discriminate a horizontal line of symbols while retaining the ability to see isolated symbols) and found that it was just as marked in the vertical as in the horizontal plane. Therefore, they disputed Cuppers' theory but endorsed the concept of poor fixation as causative. A comparison of amblyopic with ametropic eyes showed no difference in their ability to discriminate single-E and line-E acuities. The phenomenon, therefore, could not be based on amblyopia per se.

Some studies have stressed that the disturbance in the fixation mechanism and motor incoordination were related to separation difficulty (*80*).

Burian, Benton, and Lipsius (*25*) found that visual cognitive abilities in the amblyopic and nonamblyopic eye did not differ significantly and hence that amblyopia could not be classed as an agnosia.

Extraordinarily interesting microelectrode studies were reported by Hubel and Wiesel (*121, 122, 123*) on the altered electrical responsivity to light in cells of the visual cortex and lateral geniculate body of the kitten when (1) previously deprived of light either through occlusion of one or both eyes (*121*) or (2) following artificial strabismus (*122*). Monocular light or form deprivation in the first 3 months of life causes marked abnormalities of response of these cells, including sometimes irreversible cellular alterations in the lateral geniculate body (*123*).

Binocular deprivation, while permitting greater responsiveness, also resulted in marked abnormality of the responses. Artificial strabismus or alternating occlusion of the eyes gave similar results, showing that there was a loss or abnormality of response of the visual cells. A loss of synchrony of the afferent impulses impinging upon such cells of the cortex and lateral geniculate body leads to irreversible functional and structural changes. The absence of such synchronous input may lead to marked alterations of dominance, so that only the dominant eye can drive visual cells, the other eye being completely isolated from its receptor-cell population. The implications of these studies for strabismus in man are by no means clear. Nevertheless, the importance of early restoration of binocularity, at least in the cat, would seem essential for the maintenance of normal binocular visual responsiveness in the brain. It seems to lend strength to the concept of early therapy of amblyopia and strabismus in order to prevent such hypothetical (in man) changes from occurring. This is an area of extremely fruitful investigation which may lead to significant advances in the future.

Bangerter and Cuppers independently revitalized the subject of amblyopia with the introduction of pleoptic theory and practice. By means of ophthalmoscopic modifications enabling the determination of the fixation pattern, both authors described a high incidence of eccentric fixation in amblyopia. Bangerter used an ophthalmoscope with a green filter containing a pin hole. Fixation of the bright spot of light on the green background by the patient enabled the observer to note where the patient actually fixated. By means of a specially designed instrument, the visuscope (Cuppers), the patient fixates a central star surrounded by concentric rings ½° apart which are projected on the fundus. Eccentricity is readily detected and measured. Bangerter lists a number of types of fixation patterns: (1) Amblyopia without fixation; (2) amblyopia with eccentric fixation (peripheral, paramacular, or parafoveolar); and (3) amblyopia with central fixation. In addition,

fixation may be steady, unsteady, or nystagmoid in character. Most amblyopes of moderate or high degree lack steady fixation. Both workers evolved a concept of amblyopia in which retraining the fixation pattern was the goal. They enunciated two rules for treatment of amblyopia: first, to reestablish the straight-ahead visual direction for the fovea, removing this directional value from the eccentric element; and second, to reestablish the primacy of the fovea over the rest of the retina in respect to all physiologic functions, including acuity. Von Noorden and Burian believe that the eccentric retinal element becomes the zero point of retinomotor value for the entire retina, and, therefore, that it is necessary to reestablish the zero point of retinomotor value at the fovea. Bangerter employs a technique of bleaching the retina and eccentric element by dazzling light, while protecting the foveal area with a black disc. In this way, the subject is made aware of his true foveal projection. Active foveal stimulation by means of light flashes and subsequently by means of graded optotypes projected in line with the true central axis is then carried out. In addition, Bangerter devised a whole series of instruments designed to coordinate eye, ear, and touch—to support, by conditioned reflexes, a proper projectional reorientation of the eye. Bangerter's scotomization and stimulation technique may be considered passive and may be applied in younger patients. Cuppers' afterimage technique, on the other hand, is an active one, requiring more cooperation from the subject. Here, the negative foveal afterimage produced by a similar blinding technique (euthyscopy) is projected into space, and the individual is taught to reorient that projection onto targets, such as optotypes or Haidinger's brushes, so that he relearns the true straight-ahead foveal directional value.

Recent studies in pleoptics have been in the direction of increased development of instrumentation and methods of treatment. A final word on the validity of the therapy and a reliable critique of its capabilities are still not possible without considerably more analytical clinical evaluation. Perhaps the greatest contribution of pleoptics lies in the enhanced stress on better diagnostic methods.

A possibly significant development in the medical therapy of suppression and amblyopia has been reported by Bietti (*11*), who found that inhibitory scotomas decreased with oxygen or strychnine administered systemically and subconjunctivally. Bagolini and Tavolara (*7*) have confirmed these effects, which were also obtained with vasodilators and hormones.

The classical occlusion of the beter eye is still the mainstay of prevention and treatment in forcing the amblyopic eye to assume its proper level of visual acuity. The role of inverse occlusion (of the amblyopic eye) in eccentric fixation, although useful, is still not clearly defined.

In answer to the questions initially posed, one may say:

1. Amblyopia shows aspects of sensory and motor causation. The presence of a constant motor deviation of the visual axis, plus a deviation of the fixation axis (eccentric fixation), constitute the most significant desiderata. A suppression scotoma is characteristically present.
2. Amblyopia has both cortical and retinal aspects, and a dogmatic statement implicating one to the exclusion of the other is not possible.
3. The presence of some degree of eccentric fixation is extremely common, and the decrease in visual acuity produced by slight, perhaps unrecognizable, eccentricity may be significant.
4. The eccentric point may be selected by various mechanisms in different instances: better peripheral acuity, shift in visual direction (anomalous correspondence), or shift in zero retinomotor value.

Research in amblyopia must proceed along anatomic, psychophysical, and neurophysiological lines. The function and role of the retina, optic pathways, and cortical "centers" must be studied in depth.

The clinical problem of amblyopia requires a vastly heightened awareness of its existence on the part of physicians and the public, since, in general, prevention is still more effective than treatment. The effectiveness of pleoptic therapy has been demonstrated in selected cases, and it is particularly valuable in anisometropia. Although much abused, it is clearly here to stay. Careful work must be done to delineate its usefulness and improve its results.

DEVELOPMENT AND AGING OF THE OCULOMOTOR SYSTEM

There is very little precise knowledge of the developmental and aging aspects of the sensory and motor components of the oculomotor system. Here is a fruitful and vital area of research. The maturation of the physical mechanisms subserving vision, accommodation, and ocular movement, and their changes with age, are known only in broad outline. Similarly, the development and senescence of the sensory mechanisms in binocular vision are poorly understood at present. It will require teams of basic scientists and clinicians to fill in the details.

Oculomotor genetics constitutes a field for intensive research. The familial factor in strabismus, both sensory and motor, is universally recognized, but no

experimental studies are available. The association of oculomotor disorders with varied systemic dysfunctions has been cataloged in numerous syndromes. The locus and nature of the genetic defect may be determined by study of the accompanying pathology. Unfortunately, a suitable experimental animal for strabismus has yet to be found.

From ocular embryology to ocular geriatrics, a broadly based scientific program is an inescapable necessity if we are to progress in the understanding and amelioration of defects of the oculomotor system.

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Chapter 6—RESEARCH IN NEURO-OPHTHALMOLOGY

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INTRODUCTION

GOODWIN M. BREININ, M.D.

Neuro-ophthalmology is coming of age as a viable and distinct subspecialty of ophthalmology and neurology. It requires specialized training and knowledge of techniques in both areas. The main problem of neuro-ophthalmology is to create a cadre of workers in the various teaching and clinical centers of the country. The vast subject matter embraced in this subspecialty almost defies exposition. It is clear, however, that the neuro-ophthalmologist is not and must not be a superspecialist divorced from the mainstream of medicine. He is, in fact, immersed in the core of medicine, and the degree to which he is successful in carrying out his mission will reflect his competency as a "compleat physician." The eye must be seen in due proportion as part of the body, an integral participant in the ebb and flow of physiologic and pathologic processes.

The teaching, training, and research aspects of neuro-ophthalmology must be viewed within this broad perspective. Frank Walsh, the dean of neuro-ophthalmology in this country, has repeatedly stressed this fundamental and unifying concept.

THE TRAINING OF A NEURO-OPHTHALMOLOGIST

WILLIAM F. HOYT, M.D.

From a clinical point of view, neuro-ophthalmology, as a subject in ophthalmologic, neurologic, and neurosurgical training programs, is a unique area of medicine concerned with the diagnosis, understanding and, occasionally, treatment of disorders of the visual neurosensory and ocular motor systems, and the related somatic sensory and autonomic systems. The goal of clinical training for all specialties concerned with these disorders is greater competence in diagnosis and management. It is apparent that efforts to achieve this clinical goal must come from all related specialties. We must encourage development of clinical teachers from neurology, ophthalmology, and otolaryngology to acquire a parallel understanding of these disorders so that they have a common language with which to discuss them and contribute to their elucidation by application of special facility and knowledge in each of their special fields. Neuro-ophthalmology should eventually become a common ground for these specially trained academicians and should, perhaps, be renamed "oto-ophthalmoneurology" or some similarly general term. It is relatively unimportant who teaches the subject; perhaps a coordinated team within a medical school would be best.

The faculty members at all medical schools should be encouraged to develop this type of working relationship about common problems. Specially trained ophthalmologists should be encouraged to work within departments of neurology and, in like manner, neurologists with a particular interest in problems of the visual and ocular motor systems should be given appointments within the department of ophthalmology. Similar sharing of specially trained personnel should occur between otology and the neurologic and ophthalmologic specialties.

Clinical research in the visual and ocular motor systems should be conducted by members trained in all these medical disciplines with coordination by members with overlapping and common understanding of the problems. Incorporation of knowledge gained from basic research in the various fields (neuropathology, neurophysiology, neurochemistry, bioelectronics, neuroembryology; etc.) into clinical techniques and application to clinical problems should come from the coordinating effort of this specially trained group of "oto-ophthalmoneurologists."

Sound clinical advances can only arise from development of this type of reoriented faculty. Getting the right men is the first problem; the research itself can be conducted under the roof of any department that will give it a home!

Should this type of clinical specialist be educated for practice in a community? Probably not. Our goal

should be to train existing specialists and developing specialists to recognize and handle neuro-ophthalmologic problems with greater skill. Clinical neuro-ophthalmology within the medical school should remain a teaching and clinical research branch firmly attached to the neurologic specialities.

Basic research in neuro-ophthalmology will rarely come from the clinician and teacher, but rather from the basic scientist in fields such as neurophysiology, neuroanatomy, neuropathology, control systems, bioengineering, and the like. The encouragement of these scientists to do basic work closely applied to a clinical problem can only be accomplished when the level of clinical scholarship and interaction with the laboratory is greatly increased.

Thus, the major problem in neuro-ophthalmology during the next 10 years is one of training; the research will follow.

RESEARCH IN TEACHING OF CLINICAL NEURO-OPHTHALMOLOGY

J. Lawton Smith, M.D.

Since neurology, neurosurgery, neuro-ophthalmology, and neuroradiology are interdependent clinical disciplines, it is evident that they can prosper best in an environment of mutual cooperation. Furthermore, in addition to such obvious clinical interrelationships, each field must maintain close liaison with the basic sciences of neuroanatomy, neurophysiology, neuropathology, neuropharmacology, electroencephalography, radioisotopic scanning, and the like. The frequent absence of such cooperation often limits the full realization of the potential contribution of each specialty. It would appear that the simplest solution to the problems existing in the overall neurologic specialty fields might be most easily resolved by having all such fields of interest in a common department or pool. Looking at the future of neuro-ophthalmology in the United States, the first thing we should do is define the existing problems and then consider how they may be solved. Problems existing in the field today include:

1. A lack of trained neuro-ophthalmologists. A generous estimate is that there are less than 30 to 50 physicians in the United States who have received any postgraduate training in neuro-ophthalmology at this time.
2. There is a plethora of clinical neuro-ophthalmologic material which is as yet virtually untapped.
3. Neuro-ophthalmology is a slow and exacting clinical field, requiring a minimum of 1 hour per new patient on the average, and often as many as 2 hours or more. This compounds the disproportion existing between the few trained men and the overwhelming clinical needs.
4. Neuro-ophthalmology is probably the least remunerative field of ophthalmology, and this factor alone tends to decrease the number of applicants in this field.
5. Neuro-ophthalmology requires more interdisciplinary cooperation than any other field of ophthalmology. A neuro-ophthalmologist must work closely with both a neurosurgeon and neurologist, and must have access to good pediatricians and internists; hence, he is naturally drawn to a medical center rather than to a small, isolated medical community. This has necessary financial correlates with regard to the equipment that must be available to such an institution.

A new and timely approach should be considered for research in teaching of neuro-ophthalmology. It is evident that there are many pertinent questions in medical education as applied to neuro-ophthalmology for which no answer is available and for which, in many instances, no attempt has been made to find answers. Some of these questions are:

1. Who should be taught neuro-ophthalmology? Should such students be residents in ophthalmology at the second year level? Should neurology residents rotate through ophthalmology? If so, for how long and at what level of training? Should neurosurgical residents have a neuro-ophthalmology rotation? Is exposure to a weekly neuro-ophthalmology conference adequate training for ophthalmology residents before going into private practice, or is a preceptorship also needed? Can neuro-ophthalmology be taught to medical students? If so, at what level should such teaching be directed? Should this teaching be done by ward rounds on a neurology ward, attendance at neuroradiology conferences, or preceptorship with private patients? It should be obvious that these and many other questions cannot be answered scientifically at this time.
2. *How* should neuro-ophthalmology be taught? Methods in use today in this country include neuro-ophthalmology conferences lasting 1½ hours per week for all residents interested. Rotation of second year ophthalmology residents through a neuro-ophthalmologic service for periods of 2 to 3 months is a common practice when a staff neuro-ophthalmologist is available (the latter being the case in only a minority of the medical schools, however). Several postgraduate fellowships are available at this time, usually sponsored by the

National Institute of Neurological Diseases and Blindness, for a 1-year period after the candidate has finished his board eligibility training; these have proved to be the best source to date for developing full-time staff neuro-ophthalmologists. It would appear that such methods do not suffice to produce the requisite number of adequately trained physicians. The detection of such common entities as ischemic optic neuritis, Horner's syndromes, nasopharyngeal tumors, diabetic ophthalmoplegia, and aberrant regeneration of the oculomotor nerve shows a marked discrepancy between the neuro-ophthalmologist and the general practicing ophthalmologist.

In order to answer some of these questions, the following points might be made about current practice. Neuro-ophthalmology as now done in the United States is primarily a subspecialty of ophthalmology. There is increasing interest in this field among neurologists, and their approach to the field has been called ophthalmoneurology. But neuro-ophthalmology is primarily and fundamentally a discipline of ophthalmology. This is because it combines two approaches—an interest in neurologic patients with a carefully taken history and neurologic examination, utilizing, in addition, the many techniques of modern ophthalmology. Thus, unless one can use the indirect binocular ophthalmoscope, retinoscope, and slit lamp biomicroscope; knows the standards methods of ocular motility testing (Maddox rod, Maddox wing, Lancaster red-green test, red glass tests, prism diopter measurements, and the like); can test visual acuity; and can evaluate pupillary function carefully, all the interest in the world in a neurologic patient will not permit a good neuro-ophthalmologic examination.

Neuro-ophthalmology is *not* a narrow subfield that merits little consideration, but indeed is a very much larger field than ophthalmology itself. It overlaps with a very large percentage of cases seen on internal medicine, neurology, neurosurgery, otology, psychiatry, pediatrics, and ophthalmology services. A reasonable estimate would be that the majority of patients seen on a neurological or neurosurgical service can be diagnosed by a careful history and complete neuro-ophthalmologic examination.

An investigator used in teaching research should be supported by Government funds at such a financial level that it would not be necessary for him to spend time doing other work in order to supplement his income. The advantages of a research-in-teaching project would be many. Fundamental information on medical education would be obtained. Even more important, increased numbers of physicians would come out of such a project sufficiently well oriented in neuro-ophthalmology to increase the number of career applicants for this field. The demand is already crowding the very limited supply of postgraduate clinical fellowships in neuro-ophthalmology in this country. Candidates for a research-in-teaching project as outlined should be carefully selected.

In summary, the future of neuro-ophthalmology in this country appears unlimited. The time has come, however, for a strong reappraisal of proper teaching and training methods to attract and qualify adequate numbers of physicians to handle the clinical and research problems of neuro-ophthalmology.

CLINICAL AND FUNDAMENTAL RESEARCH IN NEURO-OPHTHALMOLOGY

ROBERT S. JAMPEL, M.D., Ph. D.

Neuro-ophthalmology is a conjunction of two closely related but traditionally separate medical disciplines—neurology and ophthalmology. Current interest in this field reflects a significant trend which is evident throughout medicine and science, i.e., the recognition that no sharp line of demarcation exists between the various clinical and basic sciences and that an interdisciplinary approach to problems of diagnosis and treatment will be increasingly valuable in the future. Newer techniques of diagnosis and treatment will require knowledge that transcends what is traditionally considered the domain of distinct groups of specialists. Neuro-ophthalmologists already recognize this fact (*1, 2*). The future projected growth in neuro-ophthalmology may be arbitrarily divided into two categories, diagnostic and experimental neuro-ophthalmology.

Diagnostic Neuro-Ophthalmology

Future research will eventually increase our understanding of the genetic and degenerative neurological and ophthalmological diseases. These diseases are probably caused by abnormalities of metabolism that are either inborn or acquired (*3, 4*). The acquired abnormalities may be the result of infectious agents or physical influences. These abnormalities may include an absent or malfunctioning enzyme, hormone, protein, inorganic ion, carbohydrate, lipid, or other unknown factor. Disturbances in the physical relationships between various interrelated cellular systems may exist, such as an abnormal cell membrane permeability, imbalance between osmotic and hydrostatic tissue pressure systems, and cellular heat distribution and transfer. Thus, abnormal metabolism or catabolism may be the result of chemical or physical factors, or both. Some of the abnormal metabolic factors have already been partially identified in neurological and oph-

thalmological diseases, and others will certainly follow. Examples of this are phenylketonuria, acanthocytosis, and Tay-Sachs disease (*3, 5*). It is probable that replacement or deprivation therapy will be the most effective means of treating metabolic diseases. The absent or deficient metabolite will be replaced or replenished, or metabolic systems will be modified by physical or chemical means or by the alteration of basic genetic determinants. Replacement or deprivation therapy, to be most effective, must begin at the earliest possible moment at the onset of a disease entity. This has already been proven true in phenylketonuria. Therefore, the earliest possible diagnosis of the onset of a degenerative or metabolic disease will become increasingly imperative. It is in the early diagnosis of what is now considered "subclinical" neurological and ophthalmological disease that diagnostic neuro-ophthalmology will be of particular importance. The reason for this is that the eye, of all organs, lends itself to the most thorough examination. Examination of the retina affords the only view of blood vessels and nervous tissue in the clinical examination. Also, the eye is involved in practically all systemic neurological diseases (*2*). Certain clinical defects in the eye may be quantitatively measured (*6, 8*). The ability to measure and statistically evaluate subtle clinical physiological abnormalities will help in the early diagnosis of degenerative and genetic diseases. Clinical defects will be evident when analyzed by electronic means where they might not be evident in the usual physical examination. Much work has already been done in this regard in the electromyography of the extraocular muscles, electro-oculography, optokinetic nystagmus, electroretinography, and electronystagmography. Pupillography has already been developed to the point that allows quantification of a clinical physiological function (*8*). The trend in the future will be to find means that are clinically applicable to the quantification of eye movements, and to the pathological variations in the retinal circulation as well as other ocular phenomena.

Some examples of the importance of the quantification of clinical phenomena are as follows. Measurement of the velocity of eye movements by means of electro-oculography or photography may well provide the earliest sign of Parkinson's disease. Pupillography may provide the earliest signs of the onset of the diseases of the basilar arteries. The newer visual field techniques employing evoked potentials from the occipital cortex may enable the detection of early changes in the retina and the visual radiations. Fluorescein photography of the blood vessels of the retina may give an indication of the status of the vasculature of the retina and brain (*1*).

In brief, diagnostic neuro-ophthalmology will provide quantitative methods for the "subclinical," i.e., before the appearance of obvious clinical disease signs, diagnosis of degenerative neurological, ophthalmological, and systemic diseases. This will enable the earliest possible treatment of the abnormality in the physiological systems involved by the replacement or modification of abnormal or absent genes or metabolites.

Experimental Neuro-Ophthalmology

Progress in clinical neuro-ophthalmology is directly dependent upon advances in experimental neuro-ophthalmology and experimental neurology (*3*). It is the understanding of the basic physiological mechanisms of the visual system that will enable us to devise effective and rational clinical tests and treatments. This lack of physiological knowledge has been the reason that many clinical tests have passed into oblivion after initial popularity and enthusiasm.

There is no essential difference between experimental neuro-ophthalmology and experimental neurology except that experimental neuro-ophthalmology is confined to the visual sensory and motor systems and the interaction between these two systems. The problems are the same in both fields, and progress in one will naturally lead to progress in the other.

Much excellent research has been done on retinal physiology, and eventually this will have clinical significance. The early work of Ernst Mach, which pointed the way to modern concepts of retinal inhibition and interaction between various neuronal elements, has recently been reviewed by Ratliff (*9*). The pioneering work of Hartline (*10*), Granit (*11, 12*), and others has led to our modern concepts of inhibitory and excitatory mechanisms within the retina. We now have concepts to explain the brightness-contrast effect, and temporal and spatial summation in the retina.

The great complexity of the retina in structural detail is well known from the work of Cajal and Polyak (*13*). However, much about the structural and morphological details in the retina is yet to be known (*14, 15*). The retina obviously has important integrative functions. It apparently serves as an organ to modulate and screen impulses before transmitting them to the occipital cortex. This integrative capacity has been neatly illustrated by demonstrating that certain neuronal systems of the retina have directional components and signal movement over the retinal surface in a particular direction and manner (*6, 16*).

Research is continuing into the nature of the visual pigments and into the clinical methods for

measuring these pigments in the human (*17*). New pigments in the retina have been identified, which increase our understanding of color vision. With recent advances in genetics, it may be possible in the future to predict and control the incidence of color blindness. Another clinically significant by-product of retinal research will be our understanding of the mechanisms of suppression amblyopia, which is a common clinical entity, and those of the heredodegenerative retinal diseases, such as retinitis pigmentosas and macular degeneration.

Recently, a new understanding of the morphology of the optic nerve and chiasm has been presented employing the Nauta technique (*18*). More work is needed on the fine structure of the visual system. A major clinical problem is the demyelinating diseases of the optic nerve. These diseases are probably due to abnormal immunological responses, or perhaps to a filterable virus.

Electron microscopy will be actively applied to the problems of the structure of the retina, optic nerve, chiasm, geniculate body, and visual radiations (*15*). This method will supplement ultraviolet, phase contrast, interference contrast, polarizing, or fluorescence microscopy. However, even newer means will have to be developed to understand many pathological processes involving the eye and brain, since the only satisfactory method of fixation for electron microscopy to date has been osmium tetroxide. Therefore, it is unlikely that electron microscopy will reveal any particular virus or abnormal metabolic process that could be incriminated as a cause for neoplastic or degenerative disease in the visual system. Pathological processes are dynamic and cannot be disclosed by dead tissues. Thus, there is a definite need for the refinement of pathological methods, but the nature of these refined methods cannot be predicted. The new methods will have to be applied to living tissues, and techniques employing entire living organisms will probably be necessary.

Tissue culture methods will be perfected and be applied to the nervous cells that compose the visual system (*3*). An attempt will be made to clarify the function of the glial cells by analyzing chemically individual cells in culture. These cells probably have a significant metabolic function. They may transport energy-producing substances from the bloodstream to the nerve cells and serve as important metabolic factories. Tissue culture techniques will also be used for further study of viruses which proliferate in living cells. In both neurology and ophthalmology, the herpes virus is of particular interest, since it is a significant cause of pathology.

The recent dramatic increase of knowledge in the field of genetics suggests that soon this field will be of greater clinical importance. New techniques will be devised to disclose abnormalities in chromosomes and genes.

We are entering the era of the molecular and atomic levels of research into the understanding of nervous and visual function (*19*). The field of electrons and protons and their energy transfer systems will be studied. The influence on metabolic systems of such environmental factors as radiation, toxins, nutritive substances, and hormones must be elucidated. Microchemical and microdissection methods will be employed to disclose cellular metabolic systems. The integrative activity of various structures in the visual system will be increasingly studied. The work of Hubel on the geniculate body and the specificity of reactions of individual neurons to color stimuli illustrate modern physiological methods. The circulatory system of the retina and its controlling mechanisms, both nervous and hormonal, will be better understood. In spite of new developments, one should not lose sight of the fact that much is still to be learned employing classic histopathological and physiological techniques.

Specificity in individuality of the cell groups that constitute the visual radiation in their biochemical reactions will probably be disclosed. Kety has already shown this individuality for certain groups of cells in the nervous system (*20*). Knowledge of the chemistry of the central nervous system is only in its infancy (*20*).

Steroids play an important role in the metabolism of the brain. These drugs constitute one of our main ways of treating optic neuritis. The mechanism of steroid action is unknown except for the fact that it produces a marked decrease in brain swelling. Some diseases of infants are known to result in aberrations of enzymatic reactions such as phenylpyruvic oligophrenia and galactosemia (*4*). The role of the catecholamines on the visual system will be better understood in the future (*21*). New knowledge will arise in the field of neuropharmacology and electrophysiology.

Demyelinating diseases have significant visual signs and symptoms (*22*). There is destruction of myelin sheaths, conversion of degenerating myelin into cholesterol esters and fats, sparing of the axis cylinders, hyperplasia of astrocytes, perivenous location and adventitial infiltration of plasma cells, and perivascular proliferation of macrophages. All these changes take place within the visual system.

The causes and mechanisms of demyelinating diseases are unknown and still being actively sought after. The most popular hypothesis is that demyelinating disturbances are of an allergic nature due to hypersensitivity of the nervous tissue produced by immunological mechanisms (*22*). It is believed that one or more antigens combined with one or more adjuvants produce a potent antigen. Antibodies are

produced by plasma cells which circulate in the serum and protect against development of the disease. After a certain threshold of the central nervous system is exceeded, the disease is produced by an encephalolithogenic intermediary. Possibly some other circulating factors enter into the disease picture. The demyelinating diseases which affect the visual system are multiple sclerosis and neuromyelitis optica, which affect the optic nerves, and Schilder's disease, which has an affinity for the visual radiations.

Heavy metals play important roles in the nervous system. The heavy metals such as manganese, copper, and lead tend to be toxic (*21*). These heavy metals affect the eye as well as the brain. An example is hepatolenticular degeneration, in which there is deposition of copper in the cornea. This disease is thought to be due to a deficiency of ceruloplasmin, a copper globulin normally in the blood.

A knowledge of form and structure is basic to understanding function (*3, 15*). However, although morphology might suggest or indicate a function, it still remains for physiology to demonstrate that the function actually takes place. Electron microscopy, advances in neurohistochemistry, and revival of interest in tissue culture of nervous elements have led to a new era in anatomical research. Newer staining techniques, like the Nauta, will enable the more refined exploration of interconnecting nervous tracts within the brain. It is now possible to follow the degenerating processes of nerve cells with greater accuracy and see the synaptic endings on neurons (*3, 18*). The use of radioisotopes to follow migration of cells during developmental stages will aid neuroembryology and ophthalmic embryology.

Neurophysiological techniques will elucidate function and confirm morphological interrelationships. Microelectrode techniques will reveal individual neuronal function in the retina, geniculate body, and occipital cortex (*3*). A variety of intricate techniques will be employed. Potentials will be evoked, and their distribution and target areas will be studied (*23*). Potentials will be analyzed using computers. Vast amounts of data will be digested and understood. The interrelationships between the visual system and the rest of the brain will be elucidated. The regional neurochemistry of the visual radiations will be studied. Employment of autoradiography has revealed that the visual cortex is particularly active in picking up radioactive gas.

Chemical transmission within the visual system will be further elucidated. The synapses will be studied, as will the effects of various drugs including the catecholamines (*3*).

A vital area of research will be the developmental and aging aspects of the neurosensory mechanisms. Congenital, developmental, and senescent defects may ultimately be understood and palliated through knowledge of the underlying physiopathology of the evolving function.

In summary, experimental neuro-ophthalmology will follow the lines of experimental neurology. It will only differ from experimental neurology in that it will concentrate on the visual system and will employ techniques that involve the utilization of light as the main input stimulus. The solution for problems in one field will undoubtedly have a bearing on the other. In the future, research in these fields will proceed hand in hand.

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Chapter 7—CORNEA AND CONJUNCTIVA

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CORNEA

Problems concerning corneal and conjunctival diseases and the structure and normal function of these tissues fall into as many diverse categories as those of the eye as a whole; therefore, this report deals with many different diseases and scientific problems.

The cornea is the tough portion of the anterior outer coat of the eye; it is perfectly transparent, and we see it, in others, between the lids and surrounded by the white (sclera) of the eye. The light, reflected from all objects which are seen, passes through this transparent coat on its way to the retina, which covers the interior back part of the eye where the process of vision is initiated. In addition to: (1) Protecting the delicate internal parts of the eye, and (2) admitting light to the retina, the cornea is the most important structure, which (3) focuses the light rays on the retina. Ordinarily, one thinks of the lens as responsible for this function; however, it is the device for *adjusting* the focus to near and far objects. The cornea acts as a "fixed focus" lens and is responsible for about two-thirds of the total refracting power of the eye. After a cataract extraction, the cornea is the only "lens system" in the eye. Irregularity in the curvature of the cornea gives rise to many of the problems in vision which are correctable with spectacles and contact lenses. The well-known troublesome astigmatism is due to faulty curvature of the cornea, a subject which will be discussed in another section. The cornea is rarely considered by the layman, who often does not realize that it is there because it is so transparent; yet he looks through the cornea each time he notices the color of another individual's eye, which is, of course, the color of that person's iris. The existence of the cornea becomes immediately apparent, however, when the most minute speck of dust lodges on its sensitive surface. Opacification, painful injuries, and irregularities in curvature reduce or abolish its usefulness. Causes of these d sfunctions and what may be done about them are the subject of the first portion of this report.

Diseases of the cornea are numerous, and its failure to function properly due to degenerative diseases becomes more common as the average age of our population increases. It is therefore difficult to overemphasize the importance of the cornea to vision and, thus as a factor in blindness, since the sharpness of vision, or indeed the ability to distinguish between light and dark, is dependent upon the normal structure and function of this organ as an essential pathway by which light reaches the retina. An individual may be blind because of corneal disease when the retina is capable of perfect function. Blindness due solely to corneal failure is estimated at about 5 percent in the United States and Canada. In other areas of the world, this percentage is certainly far higher. In the less well-developed countries, especially in the Middle and Far East and in parts of Africa, a very high portion of blindness is due to corneal opacity. This results, in general, from the scarring which is a normal healing process following injuries caused by infectious diseases and malnutrition. The subsequent social burden is particularly heavy because it affects younger age groups, thus depriving society of their earning power, as well as forcing them to become dependent on others. Although this problem may seem remote because it is less urgent here, it is nevertheless of enormous importance internationally. American research on blinding diseases has the opportunity of aiding those affected populations in a manner which would unquestionably reflect favorably on our national image.

Of most urgent concern is the completely undocumented, yet enormous, loss to American industry resulting from numerous small injuries or bouts with external diseases, which render individual workers nonproductive for days or weeks without, fortunately, rendering them legally blind. For this reason, the loss in manpower days is not recorded, yet it is a cause of vast loss to the individuals concerned and to American industry as a whole. Examples of this include foreign bodies, for example, metallic particles from grinding machines, or the irritation produced by fumes to which men are ex-

posed in industry. When such a minor injury is incurred, one or possibly more working days are lost. Other causes of absenteeism are infectious diseases, often characterized as keratoconjunctivitis. These remarks are intended to call attention to the appreciable loss sustained by our national economy due to diseases and injuries to the corner which, because they are often not permanent, serious, or dramatic, are not included in counts of the blind.

Corneal Structure.—The cornea consists of a tough, flexible, avascular sheet of tissue approximately 0.6 mm. in thickness. Its main constituent is connective tissue fibers which are straight and arranged in bundles to form ribbons which lie one upon the other to create a layered structure. As a result of this layering, the cornea may be split readily. The front of the cornea, facing the air, is covered by epithelial cells which are constantly being renewed by cell division. They are very regular in arrangement and are transparent. The surface of the epithelium, which forms the interface between the cornea and the air, is covered by a film of tears, a few microns in thickness. It consists of two layers, an outer fatty one, which is derived from glands of the lids, and an inner one next to the epithelium, which is watery. The tear film contains enzymes which combat certain types of infections, but its main function appears to be to form the optically smooth surface which makes the cornea an effective refracting device. The film may also be of importance in the regulation of water movement through the cornea by changes in its osmotic pressure. The corneal epithelium rests on a basement membrane, which is characteristic of epithelia. It separates the epithelium from the bulk of the cornea or stroma which, as mentioned before, consists of connective tissue fibers. A narrow surface layer of the connective tissue, named after the famous English ophthalmologist Bowman, differs from the deeper parts in that the individual fibrils are much finer, are arranged in an irregular fashion, and contain no cells. The deeper connective tissue part of the cornea contains only one major cell type, the keratocyte. Occasionally, there are other cells in the normal cornea which are invaders from the bloodstream and may be regarded as a part of the defense mechanism against invading organisms. Such cells are far less common than in other types of connective tissue. The connective tissue fibers are coated by protein and a mucinous substance called mucopolysaccharides. These materials are being renewed constantly, and serve to regulate the distance between the fibers. This is an important function on which the transparency of the cornea depends. On the inner side of the connective tissue stroma is an elastic, homogenous-appearing membrane called Descemet's membrane. It is a quasi-crystalline structure, is known to consist of collagen, is very transparent, and is the product of a single layer of flat cells located on the inner surface which separates the cornea from the inside of the eye. These cells are known as the corneal endothelium. They are very delicate, easily damaged by trauma, and susceptible to degenerative diseases. They possess a high rate of metabolism, and there is good evidence that they regulate the amount of water contained in the cornea by their metabolic activity. This function is important because its failure leads to swelling or edema, with consequent loss of transparency. All therapy and understanding of disease processes and of the functional activity of the cornea, and consequently its transparency, depend on our grasp of the corneal structure.

Basic Aspects

1. *Anatomy.*—Within the last 15 years, so many advances in methodology and instrumentation have been made that this field, once considered mature, has been completely rejuvenated. Therefore, all aspects of corneal and conjunctival anatomy must be subjected to restudy, utilizing more recent methods of histochemistry, radioautography, and electron microscopy. Such studies relate directly to our understanding of their normal function and to practical problems of surgery and therapeutics. The knowledge revealed by newer anatomical techniques is related far more precisely to function and pathology than was that of classical anatomy. The anatomical research of the 19th century found important broad applications in medicine, and there is no doubt that the newer investigations will do so as well. The finer details revealed by 20th-century anatomists do no more than barely keep pace with advances in microbiology and the chemistry of therapeutic agents. The same arguments must also be extended to apply to ocular pathology, because greater resolution of electron microscopy is now available and the use of isotopes and histochemical procedures permits introduction of functional tests into a discipline which has classically depended on interpretation of morphology to explain pathology. Work in these fields has already been widely initiated in all academically oriented laboratories in this country, Canada, Europe (especially England, Germany, France, Sweden, Finland, and Italy), Argentina, and, notably, in Japan. Areas in which research appears to be particularly needed can be summarized.

With respect to anatomy, the following questions appear to be particularly urgent:

(*a*) The relationship of corneal glycoproteins and mucopolysaccharides to each other (these materials were described in the section reviewing corneal structure) and to the collagen fibers is not known; it should be fully investigated if we are

to understand the physiology of the cornea, particularly as it pertains to fluid balance, swelling, nutrition, and transparency.

(*b*) Changes in the fine structure and histochemical characteristics of vascular, scarred corneas, dystrophies, and species differences must be determined. These studies should be done both on well-controlled and experimentally modified corneas, and also on pathologic corneas obtained clinically.

(*c*) The nerve endings in the corneal epithelium have been investigated (by British scientists) only in the mouse. Incomplete studies of the same general type have been attempted in Japan on human eyes.

(*d*) The exact physical relationship of the cells in the cornea (keratocytes) to each other is not known. It has been assumed that they form a syncytium and are connected by means of long, slender processes. That these cells are, at least, in close proximity by virtue of these processes is known. The problem is of importance to clinical ophthalmology because corneal nutrition may be mediated by an interconnecting cell system. In addition, should the cells be connected, virus particles may follow the path of the cellular extensions.

(*e*) An important area of research, which may be labeled either biophysics or anatomy, has not been properly exploited. This includes studies such as the extremely rewarding ones of Maurice in England on the physical arrangement of collagen fibers; they offer our best explanation, to date, of stromal transparency. However, the transparency of Bowman's membrane and of the epithelium, the turbidity of which is often more important in visual impairment than that of the stroma, remains unexplained.

(*f*) Growth of the cornea in a mechanical or physical sense has also scarcely been examined, except in a preliminary manner, by Coulombre. In the *clinical* sense, this is the problem of the cause of one form of myopia and of increasing refractive errors which occur during childhood. The influence on corneal curvature, which may possibly be exerted by contact lenses, should also be considered. Corneal growth is clearly influenced by genetic factors; hence, investigation of inheritance of ocular shape is required as a basis for practical or applied studies on myopia.

(*g*) The rheological properties of the cornea—its elasticity, strain-stress phenomena, and tensile strength (which should include the sclera)—as well as how the corneal tissue adapts to strain caused by scar formation, must be better understood. The few studies performed at Oxford University and by Dr. McEwen in California offer only provocative beginnings. Studies on tensile strength are particularly important in relation to surgery for cataracts in aged persons. The collagen fibers of the cornea are arranged so that they exhibit birefringence when examined with polarized light. Their birefringence changes as tension on them varies, as it does when intraocular pressure rises. Such changes might be of value as a basis for a screening test to discover cases of glaucoma and, therefore, merit careful study.

2. *Embryology.*—Again, as in the case of normal anatomy and pathology, the entire normal development of the cornea must be restudied utilizing modern techniques; namely, those of electron microscopy and histochemistry.

The enormous toll that birth defects exact from our population in terms of suffering and dollar cost is well recognized. Among these, blinding diseases are the most serious. Whereas in some organ systems, malformations lead to early death of the infant, deficient ocular development is compatible with life, although not with a fully useful one. The blind child is, therefore, a distressing problem. The needs for this field naturally include maximal effort to minimize birth defects by surgery; however, a far more practical, far-reaching approach is the effort to discover the basic causes of the abnormality in order to prevent its occurrence. This can only be accomplished by investigation of developmental stages to discover when the embryo is particularly sensitive, and to discover factors which influence development. This implies infinitely more extensive work than simply the descriptions of stages of development, which have been largely completed. Some such programs with respect to the cornea are as follows: (*a*) The interrelation of the several parts on the development of each other must be studied, e.g., epithelium with stroma; (*b*) congenital anomalies should also be completely collected and restudied. The analysis of these must now emphasize possible pathology in the mother, resulting from infectious diseases, nutritional deficiencies, and ingestion of therapeutic drugs during pregnancy; (*c*) in addition, the relationship of such anomalies to genetics must be considered and studied by application of cytological methods which reveal chromosomal aberration.

3. *Physiology.*—This is a broad and exceptionally active field, very productive at present, and with even greater hope for the future. The means by which the cornea maintains transparency are still unknown. Loss of transparency due to its swelling is probably the largest *corneal* cause of blindness in the United States, although not in the world. The normal function of the endothelium is supposed to be essential in the maintenance of corneal hydration and transparency, and its impairment is probably

the seat of the problem in pathological corneas as well as in corneal transplants. However, the manner in which these cells carry out their function, even if the assumption is true, is not at all understood or established.

One aspect of corneal physiology is of such importance that it must be emphasized. The cornea as a whole must surely be engaged in active transport, perhaps in a manner analogous to that found in other biological membranes (frog skin, bladder, etc.). The existence of this transport system has been demonstrated in vitro, in the cornea, and shown to consist of the movement of sodium (rabbit) or of chloride (frog). As a result of this movement, an electric potential is developed. These facts undoubtedly are of great importance in corneal physiology and may be directly related to the maintenance of water and electrolyte balance in that tissue. If this can be proven, its significance in clinical ophthalmology would offer an explanation of the problems of corneal swelling and haze.

The apparently insignificant film of tears which normally covers the cornea is now known, thanks to the work of Dr. Mishima, to exert profound effects on its normal hydration and, therefore, is of vast importance to the diseased and edematous cornea. The mechanism by means of which the tear film exercises its role is only just now being demonstrated. Much additional work is required before this knowledge, gained in experiments on normal animal eyes, can be applied to the human eye. The first successful steps have been made in this direction in the treatment of the painful and blinding disease, bullous keratopathy. Careful clinical trials by Drs. Dohlman and Brown are currently demonstrating the value of the earlier basic research by actual application of the results of laboratory investigations to human problems.

4. *Biochemistry.*—This area of basic research overlaps the fields already discussed. Important aspects of corneal and conjunctival biochemistry are under study especially in England, Germany, and this country. This general area and that of microbiology are those in which useful therapeutic agents are most likely to develop. It is necessary, for this purpose, to understand the mode of action of drugs if there is to be hope of avoiding untoward effects of materials administered with the intention of alleviating a disease condition. The cornea is particularly susceptible to this hazard because drugs are commonly given as "drops" on the cornea for purposes not necessarily related to a corneal disease. We must, therefore, depend on biochemical research for the understanding of how these compounds affect the function of the normal cornea. Fields of particular importance include: (*a*) Study of the metabolic turnover of separate chemical entities in the cornea—for example, chondroitin sulphate in contrast to that of keratosulphate or the glycoprotein moiety. The metabolic pathways of the cellular constituents have been the subject of some investigations; (*b*) successful initial studies of abnormal corneas have been undertaken on lipid metabolism at Harvard, and on the mucopolysaccharides by Anseth, but no systematic exploitation of clinical material has occurred. Such action depends on additional development of chemical methods, but mainly on the organization of the use of biopsy and eyebank material.

5. *Microbiology.*—In the past, this huge area has been mainly concerned with diagnostic problems, while mechanisms of normal resistance of the epithelia to invading organisms and the role of the tear film and glandular secretions have been relatively neglected. The more recent aspects of microbiological research on the cornea have been immunological. As yet, however, we do not know the relative antigenicity of normal corneal constituents (cells, glycoprotein, mucopolysaccharides)—a question which is of the greatest urgency in the corneal graft problem. The route and dynamics of entry of antibodies into the cornea is unknown. Such knowledge is fundamental to our understanding and treatment of those diseases, which may be immunologic in origin.

Clinical Aspects

1. *Wounds.*—Factors which influence the healing of epithelial wounds are partially understood because of the amount of clinical experience with epithelial abrasions—especially since a large population now wears contact lenses. These injuries serve as portals of entry for serious bacterial and fungal invasion and should not be neglected. The dynamics of wound healing, especially with respect to the rate at which surgical wounds heal, and the effect of locally applied pharmacological agents which may hinder healing, should continue to be studied. A study of how corneal scars become more transparent with time needs to be made, and the possible therapeutic value of flush-fitting contact lenses in trophic corneal ulcers, in conditions of corneal edema, in diseases such as pemphigus, and in surgical procedures where the lens provides a splint, require evaluation.

Although considerable work has been done on the cytological and biochemical changes in healing wounds, this area needs further exploration if we are to understand the factors influencing healing and attendant difficulties which often occur. The biochemical studies should be directed particularly at the rate of turnover of all components of the scar, so that the stages in formation of a normal mature scar can be known. The cornea is a model system which provides an ideal site in which to study the

processes involved in wound healing and scar formation, because it is homogenous, avascular, and transparent.

Of particular importance, would be efforts to understand the physiopathology of such severe chemical burns as those caused by strong alkalis and acids; this would have a great deal of practical importance with respect to immediate as well as late treatment. The present clinical treatment of these conditions is far from satisfactory.

2. *Surgery.*—More research, resulting in publications although not necessarily basic ones, has been expended on this field than on any other in the corneal area; yet as long as surgeons are not satisfied with their results, attempts must be made to perfect their techniques. Within the past few years, this field has received a great impetus from the introduction of excellent operating microscopes. Currently, an increasing amount of corneal surgery is done with this aid, which leads naturally to the need to develop more delicate "micro" instruments and improved suture material. This area is essentially one of applied research and lends itself to a combination of laboratory and clinical study. The reaction of tissue to implanted suture materials and plastic substances used for impermeable lamellae, or permeable prosthetic devices, and to tissue adhesives, must be evaluated, first in the laboratory and then clinically. Such studies are in their infancy and as such, understandably unsystematic. Surgery to correct refractive errors has been shown to be possible, as demonstrated by the keratomileusis of Jose Barraquer, but it has not been sufficiently evaluated clinically. It requires considerable experimental study before it should be widely attempted.

Surgical problems that are not completely in the category of technique are epithelial downgrowth and the formation of retrocorneal membranes; these are genuine practical problems which must be met by future investigations on a basic level.

By far the largest problem or complex of problems relate to corneal grafting, which, although surprisingly successful, still provides, in too many instances, unsatisfactory results. Improvements are sorely needed in methods of selecting donor material with respect not only to its viability, but also with respect to its immunological compatibility. Other means of avoiding immunological graft rejection, such as the use of immunosuppressive drugs, which are currently being investigated, must be sought.

The entire problem of tissue transplantation can be, and is, exemplified and perhaps studied to greater advantage in the cornea than elsewhere. If such problems as tissue typing could be extensively explored in this simplified system, it might be of great significance to the entire general problem of organ transplantation.

There is a very considerable residuum of diseased opaque corneas which are not suitable for transplantation, and in which attempts have been made to provide the patient with transparent prosthetic devices. Recently, some success has attended these attempts, even in clinical cases (DeVoe, Cardona, Castroviejo, Dohlman). Neither the surgical technique, the shape and size of the prosthesis, the materials from which it is made, nor the basis for selecting subjects for this procedure is regarded as completely satisfactory. We still do not understand the mechanism of the aseptic necrosis which occurs around keratoprosthetic devices. However, the promise of success given by current clinical trials requires that this area of surgical research be pressed vigorously.

3. *Infections.*—Considered in these paragraphs are infections of viral, bacterial, rickettsial, and fungal origin. It is felt that the control of these conditions has almost reached a reasonably satisfactory level in areas where education of the population, and hence sanitation and adequate medical care with diagnostic methods, are available. Therefore, the admittedly great remaining clinical problem of infectious disease may, to a considerable degree, be in the area of public health.

However, even in geographical regions where the population is relatively well off, infectious diseases still remain a problem of therapy, particularly herpetic and fungal infections. The latter problem may be accentuated by use of antibiotics and anti-inflammatory (steroid) drugs.

The recently introduced agents, such as IDU, proved to be effective when the Herpes virus was limited to the epithelial or superficial layer. However, recurrence of Herpes is reported after the use of this agent;, moreover, strains resistant to it are reported to develop. Therefore, it is particularly in these areas that research must be pressed to develop new chemotherapeutic agents.

Questions concerning the location of the Herpes virus in the cornea have not been resolved, and it is not known whether the virus resides in the corneal epithelium during the period of remission. It is also not clearly understood how the virus is transported into the corneal stroma. Studies of this kind have much bearing on the therapy of this disease.

A great deal of clinical research is still needed in order to determine the proper medical and surgical treatment of the many complications of Herpes simplex. The effect of steroids in reducing host resistance is still confusing.

The various viruses and their effects upon the cornea need much more study. The serological response of the host should be studied, and a search for antiviral agents undertaken. The epidemiology of these diseases is not well known. A closely knit laboratory-clinical study is required.

The life history, clinical course, and treatment of fungus diseases is an obvious area where future developments seem bound to occur. The cornea may well be an excellent place to study antifungal drugs. This would require a large-scale program, which has yet to be initiated anywhere.

With respect to these problems, the role of tear lysozyme in resistance to infection has not been studied adequately. The cornea is an ideal tissue on which to study interferon since it is concerned with the healing of viral diseases. Thus far, only Jones of London has shown a major interest in this interesting field. The fluorescent antibody method of diagnosis of infectious ocular disease has only begun to be explored. So far, its employment has been limited experimentally to trachoma, inclusion conjunctivitis, and herpetic keratitis. The method should prove to be very useful.

Little is known about immunologic lesions in the cornea, such as disciform keratitis, marginal ulceration, nummular opacities, and similar conditions. Immunosuppressive drugs have been used in corneal diseases such as disciform keratitis with favorable effects on the inflammatory, allergic phase, but with unfavorable effects on host resistance to the viral agent through suppression of interferon production and the like. This subject needs much investigation, and experimental animal models should be developed whenever possible.

The immunopathology of the conjunctival and limbal phlyctenule is reasonably well understood, but the pathogenesis of the corneal lesions in phlyctenulosis remains obscure. No satisfactory experimental model in a laboratory animal has yet been obtained. The simple recitation of these important needs, and the opportunities which they present, would seem to document the state of our knowledge and the steps which must be taken in the near future.

Study is necessary on the mechanism by which ocular infections are carried from infected individuals to others. This includes determination of the role of the ophthalmologist in spreading infections via instruments and solutions.

4. *Keratitis.*—Classical keratitis, such as is due to tuberculosis or syphilis, is very rare; however, keratitis of unknown etiology is encountered. Carefully planned serological and microbiological tests to determine its etiology are necessary to understand these cases, for present treatment is largely symptomatic.

In many instances, an inflammation of unknown etiology occurs in the sclera adjacent to the cornea and should be included in any consideration of corneal disease.

Sjörgen's syndrome involves both cornea and conjunctiva; it is characterized by decreased tear secretion and erosion of the cornea and conjunctiva, together with dryness of the mouth and nose and arthritis. Its etiology requires study, but even more, it emphasizes the deficiency of our knowledge of tears. Very little is known of the basic physiology or chemical composition of tears in either the normal or diseased state. Physiologic studies of the tear glands themselves are very few.

5. *Corneal Vascularization.*—The occasional vascularization of the cornea following injury is a difficult clinical problem, particularly in relation to corneal grafts. It is believed that the presence of vessels greatly increases the likelihood of graft rejection. The cause of ingrowth of blood vessels is not known, although a number of hypotheses concerning this subject have been expressed. The method of growth of the vessels is also poorly understood. Satisfactory treatment for such vascularized corneas has not been evolved, although the use of antimetabolites has been proposed, and corneal radiation is frequently resorted to without certainty of success. Therefore, systematic studies of this problem are required from the practical point of view. The detailed pathology of vascularized corneas, their chemistry, and their metabolic activities are intriguing problems, if somewhat more academic. Properly, such studies should combine and employ clinical cases and laboratory models. Very little work, to date, has been done in this area.

6. *Epithelial Erosion.*—Recurrent epithelial erosions are a difficult clinical problem. The etiology of this condition is unknown, and the current treatment is inadequate. These problems can only be investigated in patients by competent clinical research. It should be as fundamental as possible; but it must be emphasized that this condition can only be studied in the clinic, since a laboratory model has not been produced.

7. *Dystrophies and Degenerations.*—In addition to the classical dystrophies, such as Groenow's macular I and II and lattice and nodular, many types of corneal dystrophies have been reported. However, in only a very few, have histochemical or electron microscopic studies been made. Therefore, their classification still depends mainly on the clinical picture. Their pathology is poorly comprehended; the therapy is uncertain and is not based on a proper understanding of the disease. Clinicians think that many in this ill-defined group have a genetic basis which should be verified by study. The corneal degenerations as, for example, lipid keratopathy, band keratopathy, marginal degenerations, the various forms of Bowmanopathy, and pterygium are all largely unknown quantities and can be understood and finally treated only after exhaustive research at the most basic level.

8. *Therapeutics.*—Aside from the development of additional antibiotics, a systematic study of drugs

which may decrease the corneal swelling in the presence of endothelial or epithelial diseases is needed. Such a study could include pharmacological agents which augment active transport. It should also include improved hyperosmotic materials, such as polyvinylprorolidone (PVP), which might provide relief in the case of edematous corneas.

The possible use of chelating agents for the removal of precipitates of heavy metals has just begun to be investigated. Other important pharmacologic studies include ones on systemically administered drugs (such as the phenothizanes) and on the chloroquin derivatives, as well as on the many toxic compounds used in industry. The basic effects of these must be determined.

9. *Occupational Hazards.*—As new technologies develop in industry, new occupational hazards are encountered. It is necessary for the ophthalmologist to be alert to the occurrence of such hazards and to be aware of the possibility of corneal involvement long after exposure to noxious agents occurs. Radiation, radioactive materials, and microwaves, as well as new chemical irritants, are among such agents. It is impossible to anticipate the specific problems which will be encountered, but it is certain that large numbers of cases will come to the ophthalmologist's attention from industry.

10. *Manifestations of Systemic Diseases.*—The effect of a number of systemic diseases is manifested in corneal pathology. Examples are: Lupus, erythematosus, erthema nodosum, acne rosacea, keratitis sicca, cystinuria, and disorders involving mucopolysaccharide metabolism, as exemplified by Hurler's syndrome. Often these diseases are not of great ophthalmic importance, but their occurrence in the eye offers an opportunity for ophthalmic research to contribute to the advancement of medicine generally. For this reason, if no other, studies should be encouraged which involve more detailed clinical observation and pathologic examination. It is hoped that interested investigators and clinicians can join resources so as to make use of clinical material for biochemical and physiological study. There is no alternative to such a procedure because, with few exceptions, such diseases are limited to man.

11. *Nutritional Problems.*—A number of nutritional-deficiency diseases are known to produce corneal pathology. These have been documented and the needs clearly defined by MacLaren in his work on keratomalacia. They are not common in the economically advanced countries. However, in Africa, and in the Near and Far East, they constitute a serious clinical problem. The solution may seem obvious, but the possibility should not be neglected that such abnormalities, if studied, might yield important information concerning the normal nutritional requirements of the cornea.

There remains to be considered the diseases caused by the well-intentioned efforts of physicians, the iatrogenic diseases. As an example, it has been claimed by thoughtful ophthalmologists that the greatest single cause of corneal clouding is the damage to the endothelium caused during cataract extraction. The remedy for this is obvious—improvement in the techniques of cataract surgery. This must, however, be coupled with an understanding of why the endothelial cells are susceptible to damage during this procedure. Other serious examples of iatrogenic diseases are those infections, especially fungal, which may occur following therapeutic use of steroid hormones. Without doubt, when the basic factors responsible for the change in susceptibility to such infections and the nature of endothelial damage occurring in surgery are determined, another large group of blinding diseases will disappear.

CONJUNCTIVA

Except for the very extensive work on infectious diseases, the conjunctiva is a relatively neglected part of the eye. The fine structure and histochemistry of normal and pathological conjunctivae have scarcely been investigated, and our knowledge of this tissue lags far behind that of the cornea. The function and clinical significance of some of the auxiliary glands is not known. Some studies have been made on the penetration of the conjunctiva and cornea by therapeutic agents which are instilled in the conjunctival sac. However, the level of our information in this respect is still primitive. Essentially, nothing is known of the chemistry of the glandular products or the rate of their secretion under normal or abnormal conditions.

The circulation of the conjunctiva offers ophthalmologists a remarkable opportunity for investigations of the vascular system in systemic diseases, even though these may not affect the eye. This is because conjunctival vessels are the most readily studied in the living body. Capillary disease or diseases which result in blood "sludging" can best be studied by the clinical ophthalmologist, who is used to the instrumentation necessary and who regularly examines patients' eyes where signs of such disease may show before it becomes evident elsewhere.

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Chapter 8—PROBLEMS IN TRACHOMA RESEARCH

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INTRODUCTION

According to World Health (May 1965), trachoma is still the "greatest single world cause of progressive loss of sight." World Health Organization estimates made 10 years ago gave a figure of 400 million sufferers from this disease. Present WHO estimates are still larger (500 million). This reflects: (1) World population growth in this period, (2) the discovery of trachoma in populations not previously surveyed, and (3) the disappointing results of control programs, except in some European countries with high standards of living.

Although the causal agent of trachoma—a small, round elementary body 0.25μ in diameter—was seen in conjunctival epithelial cells by Halberstaedter and Prowazek in 1907, cultivation of the agent was not achieved until 1957, when T'ang and associates grew it on the yolk sac of the developing egg. This led to a revival of laboratory research on trachoma, and at the present time there are laboratories all around the world that are engaged in some sort of research on the disease. At first considered a large virus, the causal agent of trachoma has been shown to have many properties of bacteria. It is now known to belong to a large group known as the PLT (Psittacosis, Lymphogranuloma, Trachoma) group, with properties lying between those of the true viruses and those of the Rickettsia.

Trachoma is a chronic disease of the conjunctiva and cornea which causes visual and other disability by inducing scar formation in both structures. According to its extent and location, the corneal cicatrization may produce any degree of visual loss. Conjunctival scars may contribute to this by causing distortion of the lids with inturning of the eyelashes. These abrade the corneal surface and cause ulceration. When the conjunctival cicatrization is severe, it may close off the secretory ducts from the lacrimal gland and cause "dry eyes," or keratitis sicca. From this condition, corneal opacification and visual loss often result. By virtue of its chronicity, moreover, trachoma often picks up secondary bacterial infection. In such countries as Egypt, for example, superinfections with the gonococcus and Koch-Weeks bacillus may lead to much more severe corneal scarring than would have resulted from the trachoma alone.

The epidemiology of trachoma has received a great deal of attention. It is known that as a rule the disease spreads in the family as a result of close contact, as between mother or grandmother and child or among siblings of preschool age. Spread is encouraged by poverty and poor hygiene, particularly in desert areas of the world where lack of running water in homes makes normal cleansing procedures impossible. Flies and eye gnats are known to be vectors of various bacterial conjunctivitides, and most trachomatologists feel that, although formal proof is still lacking, such vectors play an important mechanical role in the spread of trachoma also.

Until the introduction of the sulfonamides in 1938, no real progress had been made with the treatment of trachoma since the days of the Pharaohs. Surgical methods to relieve lid distortions had been developed, but there were no medications for the trachoma itself other than the cauterizing agents (copper salts) that had been used by the Egyptians many centuries before Christ (Ebers papyrus, 1800 B.C.). Fortunately for the world, trachoma has shown a remarkable tendency to disappear from populations whose standards of living have risen and among whom personal and family hygiene has improved. For example, trachoma was once widespread in northern Europe, particularly in France, Belgium, and Germany after the Napoleonic wars; but in the century that followed, it diminished in this region in both frequency and severity until it was no longer an important cause of blindness. In less fortunate areas, such as the Mediterranean basin, the Middle East, and the Orient, however, it continued unabated.

In 1938, Loe and others found that trachoma responded to orally administered sulfanilamide. Later on it was shown that the disease also responded to topically applied broad- and medium-spectrum antibiotics. Treatment by either method took a long time, however, and was not always effective. When the cured patient returned to an infected household, reinfection usually occurred. In spite of these short-

comings, the sulfonamides were used effectively in such countries as Austria and England to eliminate the trachoma problem almost entirely. But in the depressed areas of the world, where the disease affected a major portion of the population, none of the sulfonamide or antibiotic campaigns have materially reduced its prevalence. In the United States, an expensive sulfonamide campaign against trachoma in our Indian population was temporarily successful, but among the tribes of the Southwest, where water is scarce and family hygiene poor, the disease later returned in full force. At the present time trachoma is still a major problem in our southwestern Indian and Mexican populations, and sporadic cases are still being seen in the white population.

Epidemiologic study of the sporadic cases in adults often fails to uncover any contact with known trachoma. To account for these cases, an attempt is currently underway to establish or rule out the genital tract as a source of the trachoma agent. It has of course long been known that the agents of the related diseases, inclusion conjunctivitis and lymphogranuloma venereum, infect both the genital tract and the eye. If a genital localization of the trachoma agent can be proven, it will of course change the present conception of the transmission of the disease.

It is now recognized that a great deal more research will have to be done before trachoma can be eradicated from depressed populations. It is true that individual cases can be treated effectively by present methods, and that if such patients are not returned to an infected household or surroundings, cure can be permanent. On the other hand, success is only temporary in such p pulations as our southwestern Indians. Among these tribes the schoolchildren are regularly treated and cured, only to return with reinfections after the summer vacation. Campaigns aimed at treating entire families are expensive, and particularly so when applied to nomadic populations like our Navajo Indians.

PRESENT STATUS OF TRACHOMA CONTROL

Present methods of diagnosis and therapy are adequate only for isolated cases of acute or subacute onset in which the clinical signs are clear-cut and for which controlled therapy under hospital or clinic conditions is attainable. Present methods are not adequate for the diagnosis of childhood trachoma of insidious onset, or for the treatment of primitive populations whose cooperation is difficult to obta n. Treatment of "captive" populations, such as schoolchildren, has only limited value since reinfection from parents, relatives, and preschool siblings is a common occurrence. Under mass conditions, as in North Africa, the Middle East, and some parts of Asia, present methods of trachoma control must be considered at best a holding operation. With our present techniques, eradication of the disease is possible only among people with high standards of living who are susceptible to health education and whose health authorities have sufficient funds to conduct trachoma control on a family basis.

It is obvious, therefore, that help must come from trachoma research if trachoma is to be eradicated, or reduced to a minimum, in parts of the world where it is now a serious problem. It is true that the disease could be expected to regress spontaneously if widespread, marked improvement in economic conditions and the general level of education, particularly health education, were to take place. It is clear, however, that in the most seriously affected areas of the world, such improvements will come slowly, and that worldwide relief from this crippling disease should not have to wait so long.

TRACHOMA RESEARCH

The current trachoma research programs that can be hoped to contribute to trachoma control will be considered under the following headings: (1) Laboratory diagnosis; (2) chemotherapy; (3) vaccination; (4) control of secondary bacterial and viral infection; (5) epidemiologic studies to uncover a means of breaking the reinfection cycle; and (6) health education.

Laboratory Diagnosis

Clinical diagnosis can be made with reasonable certainty in established trachoma on the basis of the presence of tarsal follicles, conjunctival scars, or gross pannus; but clinical diagnosis in the early stages of he low-grade, often symptomless childhood disease poses a serious problem. Such cases are often confused with folliculosis, which is a benign lymphoid hypertrophy of the conjunctiva widespread among children, or with the various forms of chronic follicular conjunctivitis which ordinarily never develop pannus or scars or any visual complications whatsoever. In the hands of the skilled observer, the recognition of the so-called "micropannus" of trachoma by means of the biomicroscope has improved the clinical diagnosis of these early cases. In many instances, however, diagnosis must still be delayed until classical clinical signs are present.

Laboratory diagnosis by recognition of the Halberstaedter-Prowazek inclusion bodies in conjunctival epithelial cells has been useful in florid cases or cases with acute onset, but the inclusions are too few in number to be of much use in old chronic

cases and in childhood cases of low activity. The method is not sensitive enough to have any value at all under field conditions. A somewhat more sensitive method of microscopic diagnosis became available when Rice demonstrated an iodine-staining glycogen matrix for the inclusion body. With this stain, the contrast is such that the inclusions can be recognized under low magnification, but even this method is not of much use under field conditions.

When Roger Nichols and his coworkers from the Harvard School of Public Health adapted the immunofluorescence technique of Coons to trachoma work, a great advance in microscopic diagnosis resulted. These researchers were able to show that trachoma inclusions in very small numbers could be detected by specific fluorescence under the ultraviolet light microscope when conjunctival scrapings were stained with fluorescein that had been tagged with trachoma antibody. These results were soon confirmed by Lavelle Hanna at the University of California and by Hans Bernkopf of Hadassah University in Israel. The immunofluorescence method is now being tested by the University of California group on trachoma among Indian children of the Southwest. The method is many times more sensitive than the old Giemsa method and represents a major diagnostic breakthrough. It should aid not only in the detection of very early cases of the disease but in determining when cure has been obtained. It is now established that some cases that appear to be clinically cured are in fact subclinically active cases that harbor the trachoma agent and could spread the disease.

Other laboratory attempts at diagnosis—for example, by cultivating the agent on the yolk sac of the developing chick embryo, by demonstrating antibodies in the serum of patients, or by demonstrating specific skin reactions to intradermally injected antigen—have not yet been signally successful. In the hands of Collier and his coworkers at the Lister Institute in London, the culture method has been successful in as high as 50 percent of cases, but it is tedious, costly, and often inconclusive, so no practical application of it is as yet in sight. Other laboratories have had a much lower success rate. A simpler and more sensitive culture method is greatly needed.

Serological tests have been even less rewarding. It has been possible to demonstrate complement-fixing antibodies in a small proportion of trachoma cases, but the test is nonspecific even when positive, since the C.F. antibodies are group antibodies and the test fails to differentiate psittacosis, trachoma, inclusion conjunctivitis, and lymphogranuloma venereum. No specific antibodies have yet been demonstrated in the sera of trachoma patients. Less rewarding still have been attempts to develop a specific skin test for trachoma like the Frei test for lymphogranuloma venereum.

Chemotherapy

No drugs more effective against trachoma than the sulfonamides (first used in trachoma in 1938) have yet been found. Attempts to use the sulfonamides locally have met with only limited success, since the sulfonamide effect is viristatic rather than viricidal and a steady therapeutic concentration must be maintained in order to obtain a cure. Since this can be done only by very frequent applications of the drug, both day and night, it is impossible under ordinary field conditions. Use of the long-acting sulfonamides, which require only one dose a day, has been moderately successful. They carry a hazard, however, since it is difficult to eliminate the drug when a drug reaction occurs.

Nevertheless, in isolated cases and in cases that can be supervised by trained personnel, as may be the case in boarding schools, sulfonamides are the treatment of choice and give the highest percentage of cures. A serious handicap is that a minimum of 2 weeks of therapy is necessary, and experience has shown that primitive populations rarely tolerate such prolonged medication unless hospitalized. Unless a sulfonamide with viricidal properties can be developed, treatment time will of necessity be prolonged, since the causal agent is eliminated only by the desquamation of epithelium. Attempts to speed up this desquamative process by the use of silver nitrate and other cauterizing agents have met only with limited success, but research along these lines is continuing at the University of California.

The action of the broad- and medium-spectrum antibiotics when used topically is no faster, but the antibiotics have several advantages over the sulfonamides, including safety. When a drug such as achromycin, suspended in oil, is used three or four times daily, a treatment time of 4 or more weeks is required to effect a cure. This regime is well adapted to schoolchildren but fails regularly in the treatment of adults and preschool children. The drug is irritating, causes temporary blurring of vision, and is soon abandoned by primitive peoples.

The intermittent treatment schedule that was developed by a World Health Organization team in Morocco has certain advantages. With this schedule, the antibiotic is used for 3 or 4 consecutive days in every month for 5 months. This is better tolerated by the patients than continuous treatment and has the advantage of preventing or minimizing the common secondary bacterial infections.

In spite of active chemotherapeutic research, no drugs superior to the broad-spectrum antibiotics and

the sulfonamides have been discovered. Such research is continuing in several laboratories, however, in the hope that new chemotherapeutic agents, alone or in combination, may shorten treatment time and in this way be more useful in mass campaigns.

Vaccination

Trachoma is a localized eye infection that often heals spontaneously, particularly in children, but which does not convey immunity. Trachomatologists feel certain that in children in endemic areas there is a process of infection, spontaneous healing, reinfection, and occasionally superinfection with the agent. It is known that some races and some individuals are resistant to trachoma infection, but total natural immunity does not seem to exist. American Negroes, for example, are remarkably free from trachoma in spite of the fact that economic conditions and conditions of personal hygiene have, in the past, been such that trachoma might have been expected to flourish among them. This immunity of the American Negro is only relative, however, as was recently shown in an accidental infection of a Negro animal caretaker at the University of California. The accidentally induced disease was mild but typical, and the agent of trachoma was isolated from it.

In spite of this lack of natural immunity and the frequent occurrence of reinfections, there is still a theoretical basis for vaccination trials. The agent of trachoma grows in the surface epithelium of the conjunctiva and cornea and has very little contact with the immunity-building tissues of the body. In vaccination, a mass of antigenic material—in this case, cultivated trachoma agent—is injected subcutaneously or intramuscularly so that the antigenic stimulus is many times that of the natural disease. This antigenic stimulus can be measured in part by determining the amount of group complement-fixing antibody.

On the other hand, the micro-organisms of the psittacosis - trachoma - lymphogranuloma venereum group are notoriously poor immunizers, and there is no example of successful vaccination against any of the numerous diseases produced by its members. However, some modification of the disease has been obtained in the case of turkey ornithosis, a serious disease in the turkey flocks of the west coast. This modification of the turkey disease is reflected in a lower mortality and a milder course.

At the moment, five major institutions (Harvard School of Public Health, Lister Institute of Experimental Medicine, University of Washington School of Medicine, the South African Institute for Medical Research, and the Instituto Superiore de Sanita of Rome) are engaged in human vaccine research. The results of these researches were summarized at a meeting sponsored by WHO in Geneva in August of this year. None of these laboratories reported striking success, but all reported that the attack rate of trachoma could be influenced by vaccination. This influence consisted for the most part in delaying the age of onset of trachoma in the vaccinated children. For example, the University of Washington group (headed by Dr. J. Thomas Grayston), in reporting their vaccination studies in Taiwan, claimed that the vaccine was 60 percent effective in preventing trachoma at the end of 1 year, but this figure had dropped to 10 percent at the end of 5 years. The Harvard group reported that the vaccination of infants in Saudi Arabia was effective in minimizing trachoma infection for a period of 6 months, but that this effect had disappeared completely at the end of 2 years whether or not booster doses were given. The South African group (headed by Dr. Graham Scott) noted that, over a 20-month period, the attack rate in 100 control children was considerably less than in a nonvaccinated group of 100 children.

The vaccination studies are complicated by the fact that more than one immunologic type of trachoma agent is usually found in one community, so that the vaccine must be polyvalent, and by the fact that live vaccine, which would be more effective, must be avoided because of the possibility that tissues other than those of the eye may be susceptible to infection with the agent.

Another serious theoretical complication of vaccine therapy has arisen. It has been shown in monkeys that incomplete vaccination sometimes induces allergic manifestations in the cornea and conjunctiva that markedly increase the severity of the disease. In studies of volunteers infected with the benign related disease known as inclusion conjunctivitis, the University of California investigators have encountered these allergic phenomena after reinfections with the inclusion conjunctivitis agents. Inclusion conjunctivitis is a disease ordinarily without corneal complications, but second and subsequent attacks are frequently associated with superficial corneal opacities which are believed to result from a combination of antibody and antigen in the cornea and which may temporarily reduce vision.

It is of interest in this connection that one theory which attempts to explain the great variation in the severity of trachoma suggests that severity is associated with the development of hypersensitivity. Hypersensitivity is ordinarily minimal or absent because of the localized nature of the eye disease. This unexpected complication of immunity raises a serious problem for vaccinators.

At the present moment vaccination holds little promise of conferring complete protection from the disease, but it does hold some promise of conferring

a relative immunity which could minimize the reinfection and superinfection problem that is so important in trachoma-endemic areas. For example, if the reinfection of treated schoolchildren could be prevented by vaccination, the whole picture of trachoma in our southwestern Indians would be modified, and an expensive and difficult family treatment program could be avoided. A combined treatment-vaccination program is therefore a distinct possibility for the future.

The WHO group concluded that continued vaccine research was very much in order in the hope of obtaining ultimately a widely applicable vaccine. It is known that some strains are more antigenic than others, and it is hoped that fractionation of antigens may yield fractions which will be highly antigenic without being toxic.

Control of Secondary Bacterial Infection

The importance of secondary bacterial infection varies greatly throughout the world but is greatest in desert and tropical areas where spring and fall epidemics of Koch-Weeks conjunctivitis add greatly to the severity of trachoma. Other bacteria, including Moraxella and staphylococci, can superinfect trachoma; in certain parts of the Middle East, there is a much-dreaded superinfection with gonococci which are highly pathogenic for the cornea and account for much blindness through the production of ulceration followed by dense scarring. Present methods of chemotherapy, although not very effective in controlling trachoma, have been remarkably useful in the control of secondary infections. Particularly valuable has been WHO's intermittent schedule of treatment with achromycin in ointment or oil, used in countries such as Morocco, where Koch-Weeks conjunctivitis is devastating. The widespread use of this method in Morocco, for example, probably accounts for the greatly diminished visual loss there, in spite of the fact that trachoma itself has not been greatly modified. Certainly this method of control should be extended to all parts of the world where epidemic bacterial conjunctivitis is a problem. Indeed, the control of bacterial infections is the only really bright spot in the overall trachoma picture.

Epidemiologic Studies

Recent epidemiologic studies by Foster of a Pima Indian village are of interest in showing the family nature of trachoma, and in showing that the peak of trachoma infection takes place before the age of eight. Foster pointed out that, while maternal infection is important, transmission from child to child in playing, wrestling, and sleeping together is also important. It has long been known that in the absence of running water, the family wash basin, and the common towel are potent forces in intrafamilial spread. Studies are now under way among the Southwestern Indians to determine the effect of the introduction of running water into a village. Presumably the chain of transmission at the wash basin will be broken, and improvement in personal hygiene in the family will be reflected in a lower transmission rate.

Another attempt at interrupting the infection cycle is being undertaken by Division of Indian Health officers in the Indian area. More than 50 percent of deliveries are now being accomplished in Indian hospitals. This gives an opportunity to diagnose and treat the maternal disease under hospital and outpatient conditions. It is felt that an adequate campaign to treat all maternity cases will result in a considerable modification of the childhood attack rate.

Health Education

Health education in primitive populations has in general been disappointing. There is little or no evidence that health education campaigns by means of posters, filmstrips, lectures, and so on have had any influence on trachoma. Efforts at health education among our southwestern Indians have been underway for many years. An excellent film by Dr. Fred Loe for use in the Navajo area was made in 1940 and is still being used. It emphasizes the role of the washbasin and towel in trachoma transmission and offers a means of minimizing this hazard. Its effect on the Indian population has not been significant. However, a steady improvement in the economic and educational status of the Indians is underway, and health education should gradually become more effective. If simple household hygienic measures could be taught, the spread of trachoma could be prevented. Further research along these lines is therefore greatly needed.

Investigations on Inclusion Conjunctivitis and Oculogenital Disease

The benign, self-limited disease known variously as inclusion conjunctivitis, inclusion blennorrhea, or paratrachoma has long intrigued trachoma investigators because of its many similarities at onset to trachoma, and because of its epidemiologic relationship to a benign cervicitis of the female and a nongonorrheal urethritis of the male. An old concept that inclusion conjunctivitis may be a simple variant of trachoma has been revived in recent years by Barrie Jones of London. Jones has claimed the production of a typical trachoma, with pannus and scars, in a human volunteer with an isolate from inclusion conjunctivitis. Our University of Califor-

nia group, on the other hand, has been able to produce only typical benign self-limited inclusion conjunctivitis with two strains isolated from inclusion conjunctivitis.

In any event, Jones' concept has stimulated much work on the subject of oculogenital disease, both in the United States and abroad. At the University of California, we have isolated one strain of PLT agent from the urethra of a trachoma case, and have studied over 30 cases of inclusion conjunctivitis with urethritis or cervicitis. It is evident that genitourinary disease caused by members of the PLT group of agents is widespread, and that an additional type of venereal disease, now known as "inclusion urethritis" and "inclusion cervitis" must be added to the already long list of such diseases.

Much research is still needed to determine whether or not tissues other than the urethra and cervix may be involved, and whether or not scars and strictures may result. PLT agents isolated from genitourinary infections must be tested on simian hosts, and the relation of these agents to trachoma, inclusion conjunctivitis, and lymphogranuloma venereum determined.

OTHER VISUAL DISORDERS RESULTING IN WORLD HEALTH PROBLEMS

Measles Keratitis

Although epithelial keratitis is a constant feature of measles in the United States, there are very few well-documented examples of subepithelial keratitis leading to scar formation and subsequent visual loss. Such cases do occur exceptionally, however, and the characteristic lesion is a disciform keratitis. In other parts of the world, however, measles keratitis can be a serious cause of visual loss and even of blindness. In Africa its serious nature seems to be related to associated vitamin A deficiency. Much work is needed to define this association and to determine whether or not there are any other associations, such as trachoma or bacterial conjunctivitis, that may aggravate the severity of this constantly occurring epithelial keratitis.

Vitamin Deficiency

Ocular changes due to vitamin deficiency are not an important cause of visual disability in the United States. Rare cases do occur, however. In California keratomalacia due to vitamin A deficiency has been seen in infants on special antiallergic diets, and all forms of vitamin deficiency have been seen in connection with chronic alcoholism. In many parts of the world, notably Central America, Africa, and the Orient, vitamin deficiency is common, and vitamin A deficiency is the most devastating for vision.

The World Health Organization has been interested for many years in nutritional problems, and involvement of the eyes in vitamin A, B, and C deficiencies has been scrutinized. Much work remains to be done on the ocular changes that occur as a result of these deficiencies; particularly we need to know more about the early diagnosis and topical therapy of malabsorption syndromes. There is much dispute concerning the role of riboflavin in ocular disease, particularly in relation to corneal vascularization, and further experimental work is needed. This vitamin has been said to play a role in chronic blepharitis and marginal corneal ulceration, but there is as yet no proof of such a relationship.

Onchocerciasis

This disease is one of the few diseases involving the eye that has engaged the major attention of the World Health Organization. It is widespread in southern Mexico and Central America, and it affects many millions of people in Africa. The pathology of the disease is now well understood, and the role of the Simulium fly as vector has been well established. These microfilaria ordinarily produce scalp nodules following the bite of infected flies. From these nodules, microfilaria migrate to the anterior segments of the eyes where a destructive keratouveitis is produced. An extensive campaign of nodulectomy is now underway in Guatemala, but the results are not yet known. Chemotherapeutic studies are producing interesting findings, but much research needs to be done on this disease which is a major cause of blindness in endemic areas.

SUMMARY

Trachoma is still the eye disease of greatest worldwide importance. It is one of the two epidemic eye diseases that have received major attention from WHO. The disease is unusual in having a world organization—the International Organization Against Trachoma—devoted to it, and in having its own special journal—the *International Review of Trachoma*. Trachoma was the subject of an international meeting of ophthalmologists and virologists that was sponsored by the New York Academy of Sciences in 1962. A second international meeting devoted to the disease was held in San Francisco in August 1966.

The Francis I. Proctor Foundation of the University of California San Francisco Medical Center has been designated by WHO as an International Reference Center for Trachoma. The Center will collect and categorize strains of the agent from all parts of the world, will serve as a training center for investigators of the disease, and will collect and make

available to all interested parties the results of investigations in laboratories throughout the world.

A major breakthrough in trachoma control will occur when new and more rapidly acting chemotherapeutic agents are developed; when an effective vaccine can be evolved; or when world economic conditions improve sufficiently to permit health education measures and simple epidemiologic control measures to be effective.

It is of interest that major trachoma studies are being conducted in all parts of the world, and particularly in such countries as the United States and Great Britain, where trachoma itself is not a major problem.

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Chapter 9—GLAUCOMA

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INTRODUCTION

The term "glaucoma" refers to a heterogeneous group of ocular disorders whose common denominator is an elevation of intraocular pressure. Such pressure elevations in susceptible eyes lead to cupping and atrophy of the optic nerve, with concomitant loss of visual field. Untreated, the process may progress to total, irreversible blindness. Present figures indicate that glaucoma is responsible for 13.5 percent of the legally blind persons in the United States.

The height of the intraocular pressure is determined by the rate of aqueous production by the ciliary body and the resistance to the outflow of aqueous humor at the angle of the anterior chamber. The effect of pressure elevation on the optic nerve is determined by the morphologic appearance of the optic disc, and functionally by careful performance of visual fields. The exact mechanism of this pressure damage, however, is unknown.

The glaucomas may be classified, in general, into primary and secondary glaucoma, depending upon whether or not the increase in pressure is related to some known antecedent or concomitant ocular disease. In general, the primary glaucomas are bilateral, whereas the secondary glaucomas are often unilateral. There is increasing evidence that the primary glaucomas are genetically determined. The following classification divides the glaucomas into four major divisions:

1. Primary open-angle glaucoma.
2. Primary angle-closure glaucoma.
3. Infantile glaucoma.
4. The secondary glaucomas.

INTRAOCULAR PRESSURE

The intraocular pressure (P_o in mm. Hg.) varies directly with the rate of secretion of aqueous humor (F in μl/min.) and inversely with the facility of outflow (C):

$$P_o = F/C + P_v$$

where P_v is the episcleral venous pressure (mm. Hg) (*11*).

In the normal eye, variations in aqueous secretion related to diurnal fluctuations, endocrine disturbances, hydration, drugs, surgery, and so on, result in alterations in intraocular pressure. These are usually small and are accompanied by what appear to be compensatory adjustments in outflow facility, which maintain a relatively constant intraocular pressure. In most eyes with open-angle glaucoma, the outflow facilities not only are reduced but are also much less adaptable. This results in a rise in pressure and greater fluctuations of intraocular pressure with alterations in aqueous secretion (*2, 3, 6, 11*).

Intraocular Pressure

Intraocular pressure is measured clinically by use of the Schiotz or applanation tonometer. In Schiotz tonometry a standardized instrument is applied to the cornea, and the depth of indentation of the cornea by the plunger under a given weight is determined. Friedenwald (*7*) postulated that change in *ocular* volume (ΔV_s) varied as a log function of intraocular pressure in the living eye. When P_o is raised to P_t by applying the tonometer, the volume of corneal indentation (V_c) is assumed equal to the distention of the sclera (ΔV_s):

$$\log P_t/P_o = E\Delta V_s = EV_c$$

where E = coefficient of ocular rigidity

$$\text{or } \log P_t - \log P_o = EV_c$$

Using a mean value for E of 0.0215 and experimentally measuring V_c and P_t, tables of P_o have been calculated (*10*).

In applanation tonometry (*12*), the intraocular pressure is measured directly as the force required to flatten a standard area of cornea (3.06 mm. diameter). The method is not dependent upon alterations in ocular rigidity, since the tonometer does not displace much fluid or significantly increase the pressure in the eye. Other methods, utilizing essentially the same principle and incorporating the advantage of fast electronic recording of the applied

force, have also been developed. These include the Mackay-Marg and the pneumatic tonometers.

In spite of a large number of surveys, the statistical characteristics of the frequency distribution of intraocular pressure in the general population are far from clear (*18*). Many of these surveys have been biased, either by overloading them with glaucoma patients or suspects, or by excluding these groups. In general, the available distributions show a deviation from the Gaussian curve, with a skewness toward the higher levels of intraocular pressure. Careful analysis of some of these studies reveals that this skewness is partly due to a significant increase in intraocular pressure with age, and that after the age of 40, females have higher pressures than males. These two factors divide any population into a number of statistically different subpopulations with different means and standard deviations, so that pooling them will produce a non-Gaussian distribution. Furthermore, individuals with a family history of glaucoma have been shown to have statistically different distributions of pressure from those who do not have such family history (*57*). The diurnal variation of intraocular pressure and the exaggeration of this variation in glaucoma further handicaps the correlation between intraocular pressure level and visual field loss in glaucoma. These factors make it impossible to give meaningful Gaussian statistics that describe the distribution of intraocular pressure in the general population. With this in mind, one can roughly say that the average value of intraocular pressure in the general population is around 15.5 mm. Hg. The problem is further complicated by the fact that different individuals vary in their susceptibility to damage by elevations of intraocular pressure. More precise methods are needed to determine this susceptibility of individual eyes to damage (*31, 68*).

Outflow Facility

Outflow facility can be measured in several ways, most of which have certain built-in assumptions and sources of error:

1. *Perfusion.*—In this method, fluid is perfused through the eye at different pressure levels, and inflow pressure P_I (mm. Hg) is plotted against inflow I (μl/mm.). From the slope of such a plot a measurement of C is obtained. For human eyes, mean values of approximately 0.28 μl/min./mm. Hg are obtained by in vitro perfusion (*1, 14, 24*).

2. *Perfusion by Abrupt Rise in Pressure.*—The introduction of a known volume of fluid into the eye produces a sudden rise in intraocular pressure. The time course of the decrease in pressure which follows this disturbance of equilibrium can be utilized to estimate outflow facility (*19, 20*).

3. *Fluorescein Studies.*—This method involves the turnover of intravenously administered fluorescein in the anterior chamber aqueous. Values for outflow facility in normal human eyes average 0.33 (*2, 11*).

4. *Tonography* (*2, 3, 13, 14, 18, 23, 52, 64, 67, 74*).—This is the most commonly used method at present for estimation of outflow facility. It is performed by placing a Schiotz tonometer on the eye for a period of 4 minutes and recording the progressive indentation of the cornea by the plunger. The pressure in the eye is abruptly raised from the undisturbed state (P_o) to a higher pressure (P_t), and the pressure-decay curve recorded. During the 4 minutes while the tonometer is resting on the eye, a volume of fluid (ΔV) is expressed from the eye. The rate at which this occurs is a measure of the outflow facility (C).

$$C=\frac{\Delta V}{4\,(P_{tav}-P_o)}$$

where P_{tav} is the average intraocular pressure during tonography. The change in volume, ΔV, is the sum of the decrease in ocular distention, ΔV_s, and the increase in corneal indentation, ΔV_c, during the 4 minutes of tonography. Studies by Linner (*21*) demonstrated an average increase in venous pressure of about 1.25 mm. Hg. during tonography. Taking these into account, the above formula becomes

$$C=\frac{\Delta V_s+\Delta V_c}{4\,(P_{tav}-(P_o+1.25))}$$

Many assumptions are made in tonography, and there are many possible sources of error. In spite of these errors, tonography provides an estimate of outflow facility in the living eye which compares closely with values obtained by other methods. The average outflow facility in normal eyes measured tonographically is 0.28 ± 0.05 μl/min./mm. Hg.

5. *Constant Pressure Tonography.*—In this procedure, P_t and ocular distention (ΔV_s) are kept constant during tonography, and all volume changes are estimated from corneal indentation (ΔV_c). Errors induced by variations in ocular rigidity and pressure-decay artifacts are, hopefully, eliminated by this method. Considerable research and instrumentation are necessary to perfect this as a clinically useful method, but it is potentially an accurate way to measure outflow facility free from many of the errors in present forms of tonography.

6. *Suction Cup* (*6, 20, 22*).—Occluding the outflow with a suction cup set at minus 50 mm. Hg pressure for 15 minutes raises the intraocular pressure. After the cup is removed, intraocular pressure is measured at frequent intervals to determine the rate at which it returns to its steady state. This figure can be converted to volume of aqueous leaving the eye, and an estimate of outflow facility obtained.

In enucleated eyes, about 75 percent of the resistance to outflow is in the trabecular meshwork (*69*).

Microscopically (*16, 25, 28*), the meshwork is made up of layers of superimposed perforated sheets between the anterior chamber and Schlemm's canal. These trabecular sheets are characterized by a central core of collagen surrounded by a homogeneous matrix containing loosely arranged collagen fibers. A layer of endothelial cells covers the sheets and is separated from the collagen core and ground substance by a thin basement membrane. The perforations near the anterior chamber measure 40μ to 60μ and contribute little to the resistance to aqueous outflow in the normal eye. Between each layer there are relatively large intertrabecular spaces which communicate with each other through openings in the sheets. The major resistance to aqueous outflow appears to be in the juxtacanalicular connective tissue which is of variable thickness (1–8μ) and consists of endothelial cells in an amorphous mucopolysaccharide ground substance containing collagenous filaments and fibrils. Although no well-defined aqueous channels are present in the juxtacanalicular tissue, a system of less organized extracellular intercommunicating spaces can be identified reaching to the inner wall of Schlemm's canal. Here a single continuous layer of endothelial cells forms a barrier to the lumen of the canal. Large vacuole-like spaces are present within these endothelial cells. Using serial sections, Holmberg (*16*) has demonstrated that these vacuoles are actually channels through the endothelial cells connecting the trabecular spaces with the lumen of Schlemm's canal. Their openings to the trabecular meshwork have a diameter of 2.5μ–3.0μ, and the opening to the lumen of Schlemm's canal varies from 0.3μ–2.0μ. These channels or pores have a diameter and prevalence which would account for the resistance to outflow in the normal eye. Whether these channels represent fixed structures or a variable functional state of the endothelial cell is unknown. Other electron microscopists have been unable to verify the continuity of the vacuoles as discrete channels, and postulate that they represent pinocytotic vesicles. Most investigators feel that the reduced outflow facility of primary open-angle glaucoma will ultimately be found to be due to alterations in the juxtacanalicular tissue.

Recent studies have demonstrated the existence of a uveoscleral system of outflow channels in the rabbit and monkey eye. The significance of this pathway and its presence in the human eye have not yet been elucidated.

Outflow facility declines with age in both animal and human eyes (*24*). The decrease appears to be due to a structural change, for it persists in vitro as demonstrated by perfusion. Corticosteroids, especially when applied topically, result in considerable decrease in outflow facility and increase in intraocular pressure in susceptible eyes (*47, 48, 49, 50, 55, 56, 58*). The degree of responsiveness to steroids is greater in glaucomatous eyes and appears to be genetically determined. Alpha-chymotrypsin, when introduced into the anterior chamber in vivo, produces a marked, temporary impairment of outflow facility and increase in intraocular pressure (*105*). Details of the pathogenesis and nature of the damage to outflow channels are as yet unknown. The hemodilution induced by the consumption of large volumes of water also results in impaired outflow and increased pressure (*54*). This effect appears to be related to the degree of hemodilution induced and is most marked in glaucomatous eyes. Outflow facility can be increased by parasympathomimetic and anticholinesterase agents. This effect is the basis of medical therapy in open-angle glaucoma (*18, 19, 52, 67, 69, 71*).

Aqueous Secretion and Flow (*1, 3, 5, 8, 9, 11, 17*)

Aqueous humor is a relatively cell-free, protein-free, clear fluid secreted by the ciliary epithelium into the posterior chamber. It passes through the pupil into the anterior chamber and leaves through the trabecular meshwork to Schlemm's canal and the venous system. During its passage through the eye, its composition is altered by diffusional exchange with the blood, by the metabolism of the ocular tissues, and by active transport processes out of the eye. Compared with plasma concentrations, the aqueous of the human and monkey eye has an excess of hydrogen and chloride ions and a deficit of bicarbonate ions. In the rabbit eye, bicarbonate is in excess, and hydrogen and chloride in deficit. Several species studied have large excesses of ascorbate and lactate in the aqueous.

Microscopically (*15, 28*), each ciliary process consists of a double layer of epithelium covering a connective tissue stroma rich in thin-walled capillaries. The outer, pigmented epithelial layer rests on a typical basement membrane, while the membrane covering the nonpigmented epithelial layer (the internal limiting membrane) is more complex. The apical surfaces of the two cell layers abut directly upon one another and are united at numerous points by junctional complexes. At the inner, free surface of the nonpigmented epithelium, multiple-microvillous processes project from one cell to another, producing a series of complex interdigitations, each covered by the internal limiting membrane. These multiple-membrane folds are characteristic of cells involved in salt and fluid transport, and are probably of considerable importance in aqueous production. Aside from the membrane folds, the most striking feature of the cells, especially in the nonpigmented layer, is the large number of mitochondria found in the cytoplasm. Other cytoplasmic organelles are also present, including the Golgi complex

and endoplasmic reticulum, though less well developed and not as numerous as the mitochondria. A large number of pinocytotic vesicles are found near the free surface of the nonpigmented cells. The dramatic increase in these vesicles following secretory inhibition by Diamox suggested that they might play an important role in secretion. Recent studies, however, suggest that they are fixation artifacts and are not found in glutaraldehyde-fixed tissue.

The secretion of aqueous is an energy-requiring process which is temperature dependent and requires oxygen. Several transport systems have been demonstrated or postulated to explain the composition and rate of production of aqueous humor. Friedenwald postulated a barrier between the epithelium and stroma of the ciliary body, with an electron transport system across the barrier (*8*). The bicarbonate system serves as a buffer on both sides of the barrier and requires the enzyme carbonic anhydrase for efficient function. The inhibition of this enzyme would be expected to reduce aqueous production (*1, 17*).

Another speculative approach supposes that carbonic anhydrase plays a direct role in the transport process. On this basis, it is postulated that hydrogen ions (in the human eye) or bicarbonate ions (in the rabbit eye), produced from carbon dioxide and water in the presence of carbonic anhydrase, are transported into the aqueous.

Bonting (*4, 75*) postulated that the enzyme sodium-potassium adenosine triphosphatase, present in the ciliary epithelium, resulted in transport of sodium across the ciliary epithelial-cell wall into the aqueous, carrying water with it.

There are at least five other transport systems into the eye, including those for ascorbate, sugars, neutral amino acids, basic amino acids, and acidic amino acids. Other systems transport substances out of the eye, including iodide, amino acids, and several larger organic anions.

Methods of measuring aqueous flow include turnover of test substances, the determination of steady state chemistries, fluorescein appearance time, tonography, and the suction cup. While each of these methods is subject to considerable error, there is reasonably good agreement, suggesting a rate of flow in the normal human eye of 1.5–2.0μl/min. This rate is subject to alteration, both spontaneous and induced. Aqueous flow varies spontaneously in diurnal fashion, resulting in diurnal fluctuations in intraocular pressure. Little is known about the details of metabolic, hormonal, vascular, neurogenic, and psychogenic factors which alter the secretory rate. The rate decreases with age, with a particularly sharp decline after 60, and is intermittently decreased in glaucomatous eyes. Several drugs, including carbonic anhydrase inhibitors, epinephrine, and cardiac glycosides, significantly reduce aqueous production. The rate is also reduced in carotid occlusion and uveitis, and temporarily reduced by ocular surgery and retinal detachment. Rapid increase in intraocular pressure produces a small but significant reduction in aqueous production. Such a change in the rate and aqueous flow during tonography would be falsely interpreted as an increased outflow facility, and has been termed "pseudofacility." Since all present methods of measurement of outflow facility involve alteration of intraocular pressure, pseudo-facility may be an important factor in accurate determination of outflow.

SUMMARY

Intraocular pressure varies directly with the rate of aqueous secretion and inversely with the facility of outflow. It can be measured most accurately by direct cannulation of the anterior chamber. Clinically, applanation tonometry gives the most accurate estimations of intraocular pressure. Aqueous production occurs in the epithelial cells of the ciliary body. The exact mechanism of the secretory process is unknown, although several separate transport systems are involved. Alterations in each can be measured. The several clinical methods of measurement of outflow facility all introduce considerable error. These include changing blood volume in the eye, variations in ocular rigidity, alterations in aqueous secretion, and various calibration problems.

PROBLEMS

Methods of Measurement

Intraocular Pressure.—As noted above, applanation tonometry gives the most accurate estimation of intraocular pressure, and the measurements agree well with those obtained by direct cannulation of the eye. The instrument, however, is expensive, and a slit lamp is required for its use. Hand-held portable applanation tonometers have been developed, but they have not received thorough evaluation and are often difficult to use. Easier methods of measuring intraocular pressure, probably utilizing the principles of applanation tonometry, are needed. The recently developed Draeger applanation tonometer appears to meet the requirements for a small hand-held instrument which is accurate and relatively easy to use. Further clinical evaluation is in progress.

Progress in this field needs to proceed along two main lines of inquiry. One is the clinical, in which the objective is to provide a method of measurement of intraocular pressure which is accurate, which is simple to use in a routine manner in the clinic and in population studies, which provides a measure of intraocular pressure that is least confused by other

properties of the eye, and which will be applicable to a large majority of the population and to all age groups. Significant in this respect may be the development of an instrument capable of measuring intraocular pressure without local anesthesia or contact with the eye, which requires a minimum of skill, and which involves no risk of damage to the eye. The other direction of investigation is for methods to aid basic research, and would aim at providing measurement of those physical and biological attributes of the eye that can influence intraocular pressure and its dynamics. The accurate determination of such factors would permit the study of their variation and significance in the health of the eye.

Outflow Facility.—The development of more accurate, clinically applicable methods of estimation of outflow facility is of prime importance in the future study of glaucoma. All of the methods presently utilized introduce considerable error and assumptions. The viscoelastic properties of the ocular coats (ocular rigidity) represent a major problem and one of the largest sources of error when the steady-state dynamics are disturbed. Recent development by McEwen and coworkers (*22*) of an electrical analog of the mechanical aspects of regulation of intraocular pressure has permitted, for the first time, a reconciliation of tonography and suction-cup data. The application of this method to the glaucomatous eye may well provide additional clues to the pathogenesis of this disease. Tonography is practical, and the values of outflow facility obtained are especially useful, but fundamental studies are needed to understand and correct the errors and artifacts of the method. In addition to the viscoelastic properties of the ocular coats, which constitute an important source of error, assumptions that have to be made whenever the steady-state dynamics are disturbed constitute a major source of uncertainty. Of these, the assumed constancy in inflow rate and in outflow facility during the disturbed steady state are of great significance. A measure of outflow facility which is independent of assumptions pertaining to inflow rate, or a measure of inflow rate which does not involve assumptions pertaining to outflow facility, will markedly refine our investigation of the physiology and physiopathology of outflow facility and the inflow process.

Epidemiologic Studies.—Epidemiologic studies that are aimed at improving our understanding of the beginning and natural history of the disease and of its prevalence are of the utmost significance. Such studies involving human subjects have been difficult to perform in the past, mainly because of organizational problems, as well as cost. It should be emphasized that glaucoma is a human disease and that the characteristics of the disease in humans must be determined insofar as possible by appropriately designed and meticulously conducted epidemiologic investigations. These include attempts to determine the frequency distribution of the various measures of outflow facility, intraocular pressure, rate of formation of aqueous, visual field findings, and the like—studies that are capable of unfolding the complex frequency distribution of intraocular pressure and determining the biologic factors responsible for it. These studies will provide reliable indices of statistical frequency and produce valuable clues as to the areas that require exploration regarding intraocular pressure. They will also provide essential material for further quantitative genetic studies. They will, in addition, provide the basic foundation to test the hypothesis that eyes that will develop glaucoma in the future belong to a distinct and separate population that could be detected early, before the complete picture of the disease becomes manifest. In a similar manner, the prevalence of glaucoma is far from being correctly established. This is due primarily to the absence of valid criteria to describe the beginning of the disease and help evaluate its true prevalence. Prospective studies aimed at long-term followup of individuals with no glaucoma, but with different intraocular pressures and outflow facilities, will be invaluable in determining whether such measures can predict later glaucoma and thus, indicate the beginning of the clinical disease. Better surveys, which are repeated at regular intervals and which include rigid followup for periods of 20 to 30 years, are required. Studies such as the Collaborative Glaucoma Study, if continued long enough, may help considerably in solving this problem.

Physiologic Investigations.—Factors responsible for fluctuation in aqueous secretion, outflow facility, and intraocular pressure are very poorly understood; nevertheless, they are of major importance. Diurnal variations of these parameters exist, but the regulatory mechanisms are unknown. The effects of hemodilution on outflow facility and pressure, and especially its correlation with anatomic changes occurring in eyes susceptible to these alterations, require considerable study. The increase in intraocular pressure with age in some eyes and the associated reduction in outflow facility need to be studied from the standpoint of the possible failure of a regulatory process which existed earlier in life. The notion that a regulatory mechanism exists which maintains intraocular pressure at a constant level and which may become upset or deficient and thus lead to the development of hypertension has not been thoroughly investigated, primarily because of difficulties in methodology.

Electron microscopic studies indicate that aqueous secretion is probably closely related to the interdigitations between epithelial cells. Anatomically, the nonpigmented epithelial cells are much more com-

plex than those of the pigmented cell layer. The relationship between these two layers of cells is unknown. Anatomic studies following modifications of transport systems known to be present in the ciliary epithelium are needed. These may elucidate the roles of the pigmented epithelium in aqueous secretion.

Recent electron microscopic studies have added considerably to knowledge of the trabecular meshwork. Much additional work is required. The presence of neural elements in the trabecular meshwork and the finding of plasma cells near the inner wall of Schlemm's canal raise questions as to their role in trabecular function and disease. The alterations occurring in the juxtacanalicular tissue in eyes with early open-angle glaucoma are unknown. Similarly, the manner in which pharmacologic agents alter the anatomic structure of these tissues is unknown and needs study.

Transport Systems.—Several systems, transporting substances into and out of the eye, are involved in the aqueous secretory process. Other systems almost certainly remain to be discovered. The exact functions of these systems, nutritional and otherwise, are unknown, but their elucidation may hold the key to the understanding of glaucoma as well as diseases of the lens, cornea, vitreous, and retina. Considerable knowledge of transport systems involved in other human diseases is rapidly being accumulated. This information plus data on the mechanism and nature of the diseases involved, should be applied to the investigation of aqueous secretion.

In view of the prominent role played by carbonic anhydrase in the secretion of aqueous humor, it would be interesting to determine qualitative and quantitative alterations of this enzyme in patients with and without glaucoma.

Experimental Animal.—Knowledge of glaucoma, both diagnostic and therapeutic, has been partially hampered by the lack of an experimental animal with the disease. Considerable effort has been made to develop a strain of glaucomatous rabbits, and this attempt has met with some success. The disease produced in these animals bears many similarities to human glaucoma, but it also has important differences. The availability of a laboratory animal with spontaneous glaucoma resembling human primary open-angle glaucoma more closely would be of considerable help in further understanding of the disease.

OPHTHALMOSCOPY AND PERIMETRY

Ophthalmoscopy provides a visual measure or estimate of the damage that increased intraocular pressure may produce in the optic nerve head. Perimetry permits a functional evaluation of the extent of that damage. In addition to being of great diagnostic value, these determinations provide the final criteria of success or failure in glaucoma therapy.

The axons of the retinal ganglion cells join as a common cable at the optic disc. As they turn back to form the optic nerve, a central funnel-shaped depression called the physiologic excavation is left in the middle of the optic disc (*29, 33, 37*). If the posterior scleral foramen is small, the axons are crowded together and the physiologic excavation is small or absent. If a large posterior scleral foramen is present, the physiologic excavation may occupy more than half the disc. When glaucomatous cupping of a disc occurs, the width and depth of that cup will depend at first on the configuration of the disc before it was damaged. Early pathologic cupping is particularly difficult to recognize in the myopic disc because of certain anatomic relationships. These include the presence of a temporal scleral crescent, the shallow placement of the cribriform lascia in the optic canal, and the exaggerated obliquity of this canal in myopic eyes.

The central retinal artery nourishes the retina and in most instances contributes to the blood supply of the optic nerve. In the development of a glaucomatous excavation, both the central retinal artery and vein become displaced nasally due to destruction of neural and glial tissue. It seems probable that the nerve destruction which results from glaucoma is based upon vascular insufficiency to the nerve head rather than upon direct pressure against the axons (*31, 32, 38*). The reason for this vulnerability at the optic disc is probably the peculiarity of its blood supply (*30, 32, 34, 36*). At the disc, an arterial anastomosis between twigs from the pial vessels, plus intrascleral twigs of the short posterior ciliary arteries, branches of the central retinal artery, and/or the central artery of the optic nerve, form the circle of Zinn-Haller. This anastomosis is under the influence of the intraocular pressure, whereas those behind the lamina cribrosa are not. An increase in intraocular pressure or a decrease in intraneural arterial pressure can permit shunting of blood away from the disc (*31, 36*). This may lead to degeneration of the glial supporting tissue and the neurons, resulting in disc cupping and nerve fiber-bundle field defects. Why these defects follow such a characteristic pattern is still unknown.

Whether caused by vascular insufficiency, intraocular pressure excess, or a combination of both, the visible damage to the optic nerve occurs at the optic disc. In the region of the lamina cribrosa, destruction of nerve fibers and glial tissue increases the size of the physiologic cup. Initially the destruction occurs in front of the lamina cribrosa, but in advanced glaucoma the process extends into the neural and glial elements behind the cribriform plate. The

lamina cribrosa is then able to bow backward, increasing the depth of the cup.

A markedly cupped, atrophic disc is an ominous finding occurring in far-advanced glaucoma. A disc with little cupping and healthy appearing nerve tissue is prognostically more favorable, even with markedly elevated intraocular pressures.

When a field defect appears in an eye with increased intraocular pressure, it is caused by damage to a group of axon cylinders in the area of the optic disc. All the axons entering the upper half of the disc originate in ganglion cells in the upper half of the retina, whereas those entering the lower half of the disc originate in the lower hemisphere of the retina. The axons run in an arcuate course from their points of origin to the optic disc and then through the nerve to the lateral geniculate body. There is no cross communication of fibers above and below the 180° retinal meridian, thus forming the horizontal raphe (*29, 33, 37*).

All the typical glaucoma field defects can be interpreted as variants of the nerve-fiber-bundle defect and the nasal depression. The typical defect is produced by cutting the conduction pathway in a group of axon cylinders at the optic disc. This produces a scimitar-shaped field defect which arches from the blindspot around the fixation point in a 10° to 20° circle, ending abruptly at the horizontal meridian in the nasal field. When both superior and inferior nerve fiber bundles are involved, a double arcuate, or ring, scotoma is produced around the spared macular fibers. The macular fibers are usually the most resistant to pressure damage, and good visual acuity is commonly retained until the disease is far advanced. A crescent of vision in the temporal periphery may persist in terminal stages after all other areas of vision are gone.

The field loss in glaucoma follows a characteristic pattern of progression, beginning with elongation of the blindspot and depression of the nasal field and continuing to the arcuate defects described above. The scotomas then extend peripherally and centrally, eventually obliterating the entire field of vision (*29, 33, 37, 38*). Progression of field loss must be carefully measured and followed by the performance of visual fields. Most ophthalmologists follow glaucoma patients with tangent-screen perimetry. In recent years the availability of the Goldmann perimeter has permitted perimetry under standardized test conditions, including background illumination, target size and illumination, and removal of all visual clues other than the test object itself. It has been found that artifactual scotomas are sometimes produced by relatively small refractive errors. It is therefore important that central fields be performed using the patient's refractive correction. This is especially true when using the Goldmann perimeter.

Goldmann and Harrington have demonstrated increased sensitivity to functional loss in Bjerrum's area of the central field in most eyes. The beginning of the specific arcuate defects of glaucoma can be demonstrated by increasing the tension of normal eyes by pressure from the outside (*31*). This sensitivity to pressure is most marked in eyes with glaucoma. All of the early field changes may be reversible if pressure is promptly reduced. This has been dramatically demonstrated in glaucoma patients by the use of topical corticosteroids to raise the tension (*35*). More often field defects in glaucoma are permanent, but their progression can usually be halted by lowering and maintaining the intraocular pressure at normal levels.

SUMMARY

The progressive cupping and associated field loss which occur in untreated glaucoma are probably the results of vascular insufficiency to the optic disc, brought about by the effects of elevated intraocular pressure on the blood supply of the nerve head. The field loss occurs most often as arcuate defects which progress in a characteristic fashion. Reducing blood flow to the nerve or increasing intraocular pressure results in relative ischemia of the optic disc and progression of field loss. Intraocular pressure can be lowered by proper treatment and a further field loss prevented in most instances.

PROBLEMS

While the anatomic and physiologic changes occurring in the anterior segment of the eye are responsible for the elevated intraocular pressure of glaucoma, the changes resulting in visual loss take place in the posterior segment. The exact mechanism of these changes, and better ways of preventing them are among the least understood facets of glaucoma. In fact, the earliest pathologic changes in the optic nerve remain unknown, since appropriate eyes with adequate clinical data have not been available for study.

Detailed anatomic, physiologic, and metabolic studies of the ganglion cell layer of the retina and optic nerve must be undertaken. There should be a multidisciplinary approach, involving research in electron microscopy, neurophysiology, pathology, and biochemistry. Additional detailed information is badly needed about the blood supply of the optic nerve and nerve fiber layers of the retina, and particularly about the changes induced by glaucoma. The distribution of autonomic nerves to the blood supply of the retina and optic nerve needs further elaboration both from the anatomic and functional

points of view. In particular, more detailed electron microscopic studies of the distribution of adrenergic fibers would be of great interest. Similarities and differences between the optic nerve and peripheral nerves, plus comparisons with other tracts in the central nervous system, should be determined.

Investigation of the effects of pressure on nerve function may reveal important factors involved in production of field loss in glaucoma. With the production of experimental glaucoma in monkey eyes (e.g., alpha-chymotrypsin) and the successful breeding of a hereditary glaucoma in rabbits, experimental approaches are now available not only for the detailed study of pressure-induced functional and structural changes, but also for the modification of these changes by pharmacologic agents.

Clinical and experimental research is needed to determine the role of blood pressure and blood flow in the production of nerve damage and field loss. The value of ophthalmodynamometry in determining these functions should be studied. The recent availability of ophthalmodynamography provides still another tool for evaluation of the individual patient. Methods are badly needed for the measurement of blood flow in the optic nerve.

Ways of evaluating the pharmacologic effects of various substances on optic nerve function must be developed. The effects of vitamins, amino acids, hormones, drugs, and other agents on blood flow and visual function have to be determined. In addition, the effects of anoxia, hyperbaric oxygen, temperature, and altered blood concentrations of various nutrients must be explored.

Perhaps the most important area for intensive study is the susceptibility of the individual eye to pressure damage. Elevated intraocular pressure is a clue, but it does not define the disease. How to recognize the susceptible eye before irreversible damage occurs is necessary in order to know which eye to treat and when to do so.

A major question is whether damage is pressure-induced in all eyes, or whether nutritional, vascular, and/or genetic factors are the major determinants of field loss. Careful studies of progressive glaucomatous field loss at lower than expected intraocular pressures should provide important clues. The tendency for elevated intraocular pressure appears to be genetically determined. It is possible that susceptibility to field loss is also genetically determined, and not necessarily by the same gene.

Better methods are necessary for evaluation of disc changes and early field changes. Although time-consuming, profile perimetry provides a most accurate method of determining threshold sensitivity in selected meridians. It is of particular value in following the progression of field changes. It is necessary that this method be made available in more glaucoma centers and, more important, that the technique and instrumentation be made practical for the ophthalmologist treating the glaucoma patient. At present, it remains a highly sensitive research tool.

Unfortunately, all present methods of measurement of visual field loss are completely subjective, and often inaccurate in the unreliable patient. The possibility of developing objective methods of field testing, perhaps utilizing EEG and computer techniques, should be investigated. Further development and refinement of electroretinography as an objective measurement of nerve and retinal function is necessary. Field loss of the type seen in glaucoma also occurs with several other ocular diseases. Methods are needed which permit accurate functional testing specifically for glaucomatous damage.

There is a need for periodic conferences of experts in many areas to outline methods of approaching and solving the problems discussed above. These conferences should include anatomists, electron microscopists, neurophysiologists, pathologists, biochemists, pharmacologists, geneticists, and clinicians. Such conferences are needed to bring together the latest techniques and methods of investigation in all areas and to encourage their application to the study of glaucoma.

GONIOSCOPY

Gonioscopy is a method of biomicroscopic examination of the angle of the anterior chamber of the eye, where aqueous humor gains access to Schlemm's canal (*39–45*). By this method, the primary glaucomas are classified as "angle-closure" and "open-angle" glaucoma, the anomalies of the angle structures in infantile glaucoma are visualized, and the secondary glaucomas are better classified and etiologically studied.

The most important anatomic factors in regulation of intraocular pressure are contained in the anterior segment of the eye. Because of the radius of curvature of the cornea, light rays coming from the peripheral iris and angle recess undergo total internal reflection and are invisible to direct clinical examination. By use of a contact lens, however, the corneal curve is eliminated, permitting examination of the angle structures. In the Goldmann, Allen-Thorpe, and Zeiss lenses, the angle is examined by light reflected from mirrors within the lenses. (*40, 42*). With the Koeppe lens, the observer looks directly at the area of the angle under observation (*43*).

The depth of the anterior chamber is determined by the position of the lens and its overlying iris. The contour of the iris as it wraps around the lens, its point of insertion upon the ciliary body, and the pupillary size determine the width of the chamber angle. The corneoscleral trabecular meshwork through which aqueous humor percolates to reach

Schlemm's canal, the collector channels, and the anterior ciliary veins, is visible just posterior to Schwalbe's line. This latter structure represents the termination of Descemet's membrane of the cornea. Posterior to the trabecular meshwork is the scleral spur, the most anterior internal projection of the sclera, and the insertion site of the majority of the corneoscleral trabecular sheets and longitudinal muscle fibers of the ciliary body. Immediately posterior to the scleral spur is the anterior surface of the ciliary body.

In the deep-chambered, wide-angled eye, the lens is held by the zonular ligaments centered in the ring made by the ciliary body. The iris originates at the inner anterior border of the ciliary body and lies with minimal contact on the anterior lens surface. The periphery of the iris is posterior to the corneoscleral trabecular meshwork and in no way prevents access of the aqueous humor to the outflow channels. An increase in intraocular pressure in such an eye must be due to an increase in resistance to outflow or to an increase in the rate of aqueous production (*40, 44*).

By contrast, in the shallow-chambered, narrow-angled eye, the lens is well anterior to the ciliary body ring, and the iris is held more snugly against a much larger area of its anterior surface. This causes a physiologic or relative pupillary block. In such an eye, a somewhat higher pressure is required in the posterior chamber to push aqueous humor through this tight iris-lens apposition than past the looser apposition of the wide-angled eye. The slight excess aqueous pressure in the posterior chamber lifts the iris root forward. If the angle is sufficiently narrow and the iris base sufficiently distensible, the iris is forced against the surface of the trabecular meshwork, blocking aqueous flow into Schlemm's canal, and an acute attack of angle-closure glaucoma may ensue (*40, 44*).

The size and shape of an eyeball are characteristics which are genetically determined. The deep-chambered eye almost always has a wide open-angle, whereas the angle contour of the shallow-chambered eye tends to be narrow. The narrower the angle, the closer the iris comes to the meshwork, and the more probable angle closure becomes.

PROBLEMS

The ability to perform accurate gonioscopy is a necessity in the diagnosis and management of glaucoma. Routine gonioscopy should be a part of the training of all eye residents. In addition, instruction in this procedure should be made available to all ophthalmologists who have not received such training. Courses in gonioscopy are presently offered by the American Academy of Ophthalmology. Nevertheless, many patients are not gonioscoped as a routine part of their eye examination.

While the anatomic abnormalities in the trabecular area in eyes with open-angle glaucoma can be studied histologically, clinical examination of such changes is not possible at present. Efforts should be made to develop better methods of in vivo examination of the angle, improved lighting techniques, vital staining of ocular tissues, and the like. Such methods would enable the clinician to identify defective structures and correlate the findings with impairment of function. Similar correlations with histologic and electron microscopic alterations should also become available.

The angle of the anterior chamber narrows with age. Study of this progressive narrowing should be carried out to determine which eyes in the young may develop acute glaucoma in later years.

Following therapy, particularly surgical procedures, careful gonioscopy should provide data to help establish the causes for success or failure.

PRIMARY OPEN-ANGLE GLAUCOMA
(*62, 64, 66, 67, 68, 72, 74, 77, 78*)

Primary open-angle glaucoma is a chronic, slowly progressive, bilateral disease characterized by elevations of intraocular pressure sufficient to produce damage to the optic nerve in the absence of gonioscopic evidence of angle closure. It is insidious in onset and progresses imperceptibly without symptoms until characteristic field loss occurs. The disease may proceed to absolute glaucoma (blindness) without pain or other symptoms. In almost all cases (over 99 percent) the elevated intraocular pressure is the result of obstruction to outflow of aqueous humor in the trabecular meshwork-Schlemm's canal system (*2, 11, 14*). Most evidence favors the trabecular meshwork bordering Schlemm's canal as the site of major resistance to outflow in both normal and glaucomatous eyes. Pathologic changes are visible in this region in eyes with glaucoma examined histologically (*25*). The etiology of these changes and the factors responsible for their progression are unknown. The finding of gamma globulin and plasma cells more frequently in eyes with primary open-angle glaucoma raises questions of immunogenic mechanisms (*65*). In rare instances, the pressure elevation appears to be the result of hypersecretion of aqueous (*53*). Although the disease is usually described as progressing constantly, careful evaluation reveals exacerbations and remissions of the outflow impairment and pressure elevation. Cupping and atrophy of the optic disc and field loss are the result of the elevated pressure.

Prevalence

The disease is the commonest of all the glaucomas, comprising 60 to 70 percent of all adult glaucomas. The prevalence varies with the criteria used for making the definitive diagnosis, but most population surveys demonstrate a prevalence of approximately 2 percent of people over the age of 40. Higher prevalences are reported in diabetics, in myopia, in older age groups, and in glaucoma families. The disease occurs predominantly in people over 50 but is found to have a significant incidence in the third and fourth decades of life and even in the teens. No sex predominance has been noted.

Diagnosis

Presented with the classic findings of cupping and atrophy of the optic dics, characteristic field loss, elevated intraocular pressure, and open angles, the diagnosis is easy. However, since visual loss from glaucoma is usually nonrecoverable and effective treatment can avoid such loss, early diagnosis is imperative. The measurement of intraocular pressure remains the most important means of glaucoma detection. Elevation of intraocular pressure is a relative term and can only be considered abnormal on a statistical basis. Ideally, one would like to know the particular pressure which will result in damage to the individual eye. At present this information is only available retrospectively. In addition, in many glaucomatous eyes, the intraocular pressure is elevated only intermittently. Thus it is possible not to recognize glaucoma simply because the patient is seen at a time when his pressure is within normal limits.

Diurnal pressure measurements may be helpful in establishing the diagnosis. This, of course, requires around-the-clock checks of intraocular pressure. Of considerable help is the fact that, in early glaucoma, tonography may reveal impaired outflow facility, especially after the consumption of a liter of water, even when pressure elevations are intermittent. In one study, 94 percent of eyes with proved glaucoma had a P_o/C ratio greater than 100 after water-drinking (*18, 54*). This finding occurred in only 2.5 percent of selected normal eyes. This does not mean that all individauls who are otherwise normal, except for a $P_o/C>100$ after water-drinking, have glaucoma. They should, however, be considered glaucoma suspects.

The above studies can identify statistically those individuals most likely to have glaucoma. Since eyes differ in their susceptibility to pressure damage, an absolute diagnosis is possible at the present time only if it can be demonstrated that visual damage is imminent or has actually occurred. The ability to diagnose open-angle glaucoma more accurately in its early stages, without treating many eyes which may never sustain damage, is a major goal in glaucoma research (*52, 64, 74, 78*).

Because of their frequent association with primary open-angle glaucoma, several conditions should arouse suspicion and demand further evaluation for glaucoma:

1. Applanation reading 21 mm. Hg or higher.
2. Schiotz scale reading 4.0/5.5 or less.
3. Visual field changes.
4. Prominent cupping of the optic disc.
5. Family history of glaucoma.
6. Intraocular pressure elevation following use of topical corticosteroids.
7. High myopia.
8. Thyrotropic exophthalmos.
9. Central retinal vein occlusion.
10. Retinal detachment.
11. Krukenberg's spindle and/or dense trabecular pigment band.
12. Endothelial dystrophy of the cornea.
13. Pseudo exfoliation of the lens capsule.
14. Diabetes.

Heredity

Primary open-angle glaucoma has been demonstrated repeatedly to be a familial and hereditary disorder. Most observers have considered it to be inherited in dominant fashion. Offspring of glaucoma patients demonstrated 40 to 50 percent prevalence of positive water-provocative tonograms, thus agreeing well with the 50-percent prevalence of the glaucoma gene among offspring of glaucoma patients predicted by dominant inheritance (*57*). However, the finding of many glaucoma patients whose parents were entirely normal to all testing casts some doubt on this mode of inheritance.

Recent studies with topical corticosteroids have reopened the question of the inheritance pattern of open-angle glaucoma (*55*). It was found that essentially all patients with primary open-angle glaucoma responded to topical corticosteroids with dramatic elevations of intraocular pressure. In selected normal volunteers, the pressure response to topical corticosteroids appeared to be biphasic, with about 30 percent developing significant pressure elevations. Similar testing of offspring of glaucoma patients revealed that almost all developed pressure elevations. Furthermore, it was demonstrated that the degree of pressure response was also genetically determined, and it was possible to divide populations into homozygous poor responders (nn), homozygous dramatic responders (gg), and an intermediate group (ng). Since almost all patients with primary open-angle glaucoma fall into the homozygous dramatic responsive group (gg), the hypothesis has been proposed that the genes determining corticosteroid re-

sponsiveness and primary open-angle glaucoma are closely related if not identical (*56*). The hypothesis suggests that this type of glaucoma is recessively inherited and that the glaucomatous individual is homozygous. The findings in normal volunteers suggest that the responder gene is very prevalent (20 to 30 percent) in our population.

Phenylthiourea (PTC) taste-testing, in which the ability to experience the bitter taste of this compound is known to be genetically determined, was applied to glaucoma populations. Significant differences in the prevalence of nontasters were found between glaucoma and normal populations (*59*). The percentage of nontasters among patients with open-angle glaucoma was 53 percent, compared with 31 percent in unselected normal volunteers and 20 percent in poor steroid responders (nn). The nature and mechanism of the association of primary open-angle glaucoma and failure to taste PTC remains unknown. Such an association of two genetically determined traits provides unique opportunities for further speculation and study.

Therapy

The goal in the treatment of primary open-angle glaucoma is to avoid visual loss. At present this is accomplished by lowering intraocular pressure. It is rational to assume that improvement of the vascular supply to the optic nerve would be equally effective, but no such therapy has as yet been developed. There is no known cure for this type of glaucoma.

Intraocular pressure may be lowered by increasing outflow facility or by depressing the rate of aqueous secretion (*69*). Medications which act predominantly in increasing outflow facility are the parasympathomimetic (cholinergic) agents and anticholinesterase drops (*71*). The former, which include Pilocarpine and Carbachol, presumably act directly at the motor-endplate level. The latter, including physostigmine (Eserine), isofluorophate (Floropryl or DFP), echothiophate iodide (Phospholine Iodide), and demecarium bromide (Humorsol), inhibit cholinesterase, permitting local accumulation of acetylcholine. The drops are administered topically to the eye. The exact mechanism by which these agents improve outflow facility is unknown. They all produce miosis, but this is not essential for their effect on outflow or intraocular pressure. The side effects of these drugs, in addition to pupillary constriction, include headache, ocular pain, and induced myopia. With the anticholinesterase agents, systemic side effects may also occur. These include nausea, diarrhea, and sometimes severe cramping abdominal pain.

Medications which act predominantly as secretory suppressants fall into the category of carbonic anhydrase inhibitors (*69*). The most thoroughly studied and widely used of these drugs is acetazolamide (Diamox) (*73*). Other agents in this group are ethoxzolamide (Cardrase), dichlorphenamide (Daranide), and methazolamide (Neptazane) (*60*). In therapeutic dosages administered systemically, these drugs reduce aqueous production by approximately 50 percent. Their side effects, which occur with relative frequency, include anorexia, weight loss, lassitude, and depression. Less often, and associated with prolonged administration, are renal stones and ureteral colic. Skin eruptions and bone marrow depression have rarely been reported.

Topical epinephrine results in a decrease of aqueous production of some 30 percent, and its action is additive to that of the carbonic anhydrase inhibitors (*61, 79*). Recent studies have demonstrated that improvement in outflow facility also occurs. This effect may begin rapidly and dramatically and is quite common after prolonged daily administration. The mechanism of this action of epinephrine remains entirely unknown. Side effects of this drug are usually ocular and consist of reactive hyperemia, black conjunctival deposits, brow ache, allergic reactions to breakdown products, and macular edema, with reduction in central acuity in rare instances.

Cardiac glycosides also inhibit aqueous production when given systemically (*75*), but they must be used in nearly toxic dosages. At reasonable dosage levels, they have failed to cause significant lowering of intraocular pressure.

Some combination of the above medications reduces intraocular pressure to normal levels and improves outflow facility in the vast majority of eyes with primary open-angle glaucoma. When pressure and outflow can be maintained at normal levels, progression of field loss can be prevented in almost all patients. When intraocular pressure cannot be satisfactorily reduced and progressive field loss occurs, surgery is required. The surgical procedures are aimed at creating new outflow channels, usually to the subconjunctival space (filtering procedures), but also to the suprachoroidal space (cyclodialysis). Successful control of pressure is obtained in about 75 percent of cases (*62, 64, 76, 77*).

Cryosurgical techniques have recently been utilized to reduce aqueous secretion by producing necrosis of portions of the ciliary body. Control of pressure has been achieved in some instances where previous surgery was unsuccessful.

PROBLEMS

There is general agreement that primary open-angle glaucoma is associated with increased intraocular pressure and that reduction of pressure can retard or prevent visual damage. The pathogenesis of the disease, however, and the progression of events

leading to field loss and optic nerve damage are not well defined. Present methods of detection and diagnosis are unsatisfactory, since many eyes with statistically elevated intraocular pressures may never develop field loss, and other eyes with glaucomatous damage may have normal intraocular pressures due to spontaneous diurnal fluctuations. Until the life history of the disease can be accurately determined, it is impossible to establish diagnostic criteria short of visual damage. Using this as the criterion for diagnosis, however, defeats the purpose of early glaucoma detection, that is, discovery of the disease before damage has occurred so that its development can be prevented by effective therapy. Since it is well established that primary open-angle glaucoma is hereditary, relatives of patients with proven glaucoma have a comparatively greater probability of developing the disease. Following such glaucoma relatives, therefore, presents the opportunity to study the development of glaucoma from its earliest stages. This requires careful ophthalmologic examination of large numbers of people over a long period of time—probably as long as 20 to 30 years. It is only through such time-consuming and expensive prospective studies, however, that accurate methods of detection and diagnosis can be determined.

Present methods of detection of glaucoma suspects —for example, elevated intraocular pressure, tonography, and water-provocative testing—require long-term evaluation to determine their significance during the lifetime of the individual. Careful followup and repeated examination of such glaucoma suspects is necessary.

In addition to determining the natural history of glaucoma and evaluating present methods of detection, efforts should be made to develop new methods of determining which eyes are most likely to suffer damage. It seems likely that individual variation in the vascular supply to the optic nerve may be of considerable importance. New techniques are required if factors such as this are to be evaluated.

The degree of pressure response to topical corticosteroids appears to be genetically determined and closely associated with open-angle glaucoma. If this hypothesis is correct, it may be possible to identify the genetic glaucoma patient long before the actual disease develops. Again, long-term studies are needed on steroid-tested patients. The availability of an accurate genetic marker would permit studies to evaluate environmental and other factors involved in suppressing or hastening the development of the disease in those genetically predisposed.

While the capacity to respond to topical corticosteroids is genetically determined, the mechanism of this response is unknown. Various mechanisms have been proposed, such as the effect of steroids on connective tissue, mucopolysaccharides, immunogenic mechanisms, fibrinolytic activity, and so on. All of these require thorough study. Unfortunately, the material from responsive human eyes is not readily available for such experiments.

These studies could be aided considerably by the availability of steroid-responsive laboratory animals. Efforts to find such animals have thus far been unsuccessful.

Spontaneous genetic glaucoma occurs in rabbits and has many similarities to human primary open-angle glaucoma. Many differences, however, are also present. Among these is the lack of response to topical corticosteroids. Nevertheless, studies in these animals may provide valuable data that can be applied to human glaucoma. The monkey eye, being more similar to the human, would have many advantages for such studies. Investigations of possible spontaneous genetic glaucoma in monkeys would be of considerable value.

Corticosteroids are valuable drugs in ophthalmology because of their anti-inflammatory properties. Many patients would lose their vision were it not for the availability of these drugs. Their pressure-raising properties are an undesirable side effect in these patients. Efforts should be made to develop steroids which are anti-inflammatory but which do not raise intraocular pressure.

Studies suggest that the lack of ability to taste phenylthiocarbamide (PTC) is related to primary open-angle glaucoma. Certain thyroid abnormalities are also associated with alterations in PTC taste-testing. The possible relationship between thyroid function and primary open-angle glaucoma requires further investigation.

Further studies on immunogenic mechanisms and their relationship to the etiology of primary open-angle glaucoma should be carried out. Gamma globulin is present in the trabecular meshwork of glaucomatous eyes. Studies are needed to investigate the nature and mechanism of its production.

The relationship of other genetically determined factors such as blood groups and serum proteins to steroid responsiveness and clinical glaucoma should be investigated. It would be of particular interest to study the occurrence of various gamma globulins (Gm factors) in populations of glaucomatous patients as compared with nonglaucomatous patients.

Better understanding of genetic mechanisms and valuable suggestions for their application in glaucoma research might arise from a series of conferences among ophthalmologists, geneticists, immunochemists, and epidemiologists.

Further electron microscopic and biochemical studies of the trabecular meshwork are required. While anatomic abnormalities occur in glaucoma and can be visualized, most such studies have involved eyes with far-advanced disease. Few eyes with

proved early glaucoma have been carefully examined and the findings correlated with changes in pressure and outflow facility.

No reports are available on changes seen in eyes with steroid-induced glaucoma. Practically nothing is known about biochemical abnormalities in the trabecular meshwork of glaucomatous eyes. The possibility of correlating biochemical changes with degree of steroid responsiveness should be investigated. Again, the need for a responsive laboratory animal is obvious.

The need for new therapeutic approaches to glaucoma is equally as great as the problems discussed above. At present all therapy in open-angle glaucoma is aimed at the reduction of intraocular pressure. It is perfectly possible that improving the nutrition and increasing the resistance of the optic nerve to pressure damage would be more effective than lowering intraocular pressure. There is relatively little known about the biochemistry and physiology of the optic nerve, and the potential rewards from research in this area are great (see sec. III).

The mechanism of action of miotics in improving outflow of aqueous from the eye is unknown. The evaluation of new agents and their effects on outflow facility may be of considerable value in determining the etiology of glaucoma. For example, the effects of mucolytic, fibrinolytic, anti-inflammatory, and endocrine agents on outflow facility might provide clues as to the nature of the outflow obstruction. Animal and in vitro and in vivo human experiments are needed.

Why eyes develop resistance to certain miotics and later recover sensitivity is unexplained. How epinephrine affects outflow facility and lowers intraocular pressure is unknown. Allergic reactions to this drug or its oxidation products occur frequently. The mechanism of this sensitivity and how it can be prevented need investigation. Serious complications and side effects, both ocular and systemic, of epinephrine and miotic therapy must be thoroughly studied. The systemic effects of topical epinephrine (extra systoles) (*51*) and the cataractogenic effects of echothiophate (*70*) have been reported recently. These need full and careful evaluation.

New surgical techniques with greater reliability and effectiveness are needed. In an appreciable percentage of cases, current surgical procedures produce either insufficient lowering of pressure or too great a reduction with resultant hypotony. This latter complication is especially hazardous when field loss approaches fixation, and can result in loss of central vision. It is theoretically possible to develop a surgical procedure, perhaps utilizing silicone or other well-tolerated plastic implants, which would permit accurately controlled reduction in intraocular pressure and avoid the risks of current procedures.

PRIMARY ANGLE-CLOSURE GLAUCOMA
(*81, 82, 83, 85, 86*)

Primary angle-closure glaucoma is a bilateral disease characterized by abrupt elevation of intraocular pressure due to blockage of the trabecular outflow channels by the peripheral iris. This glaucoma occurs typically in hyperopic, narrow-angled eyes, which usually have shallow anterior chambers. Patients with potential angle-closure have essentially normal eyes with the exception of a shallow anterior chamber and a narrow entrance to the anterior chamber angle. Prior to occlusion of the angle the intraocular pressure may be entirely normal. A combination of circumstances seems to lead to the acute pressure elevation: A pupillary resistance to the forward flow of aqueous humor at the site of iris contact with the anterior lens capsule (relative pupillary block), a higher pressure in the posterior than in the anterior chamber, a laxity of the peripheral iris, and a possible contribution of vascular factors. The peripheral iris is displaced forward toward the trabecular meshwork, and partial or complete closure of the angle results. The above chain of events is often triggered by pupillary dilatation such as produced by mydriatic drops, dim lights, a parasympathetic suppressant (e.g., proprietary sleep-promoting drugs, Atropine for G.I. symptoms or anesthesia), and sympathetic stimulation (e.g., emotional upsets). Pupillary dilatation is important because the iris is bunched up in the already crowded angle and because the peripheral iris becomes more flexible and more easily pushed forward.

Unlike patients with primary open-angle glaucoma, patients with angle closure may have prodromal symptoms of intermittent partial closure, and usually have severe symptoms when an acute attack develops. The abrupt rise of pressure caused by sudden angle occlusion stretches the corneal lamellas and disrupts their optical continuity, causing steaminess of the cornea. The hazy cornea acts like a diffraction grating and produces concentric colored haloes around light. Ocular discomfort and unilateral periorbital headache may develop. If the pupillary block and angle occlusion are relieved, such as occurs when miosis is induced by going from a dimly lit to a brighter environment, the pressure lowers and the symptoms subside within a few hours. If, however, the occlusion persists and becomes complete, the symptoms become more severe. The pressure rises to extremely high levels (often to 70–100 mm. Hg), corneal epithelial edema develops, vision is reduced, the pupil becomes fixed in mid-dilatation caused by paralysis of the pupillary sphincter, and

marked venous engorgement of the conjunctival vessels occurs; the pain becomes intense and is often accompanied by nausea and vomiting, and the optic nerve head becomes hyperemic and edematous as a result of the generalized vascular congestion. If the iris remains in contact with the trabeculum for several hours with the eye markedly congested, permanent adhesions between the two structures may develop and the outflow facility may be permanently impaired even if the attack is broken. Marked visual loss and even total blindness with cupping and optic atrophy may occur if pressures are permitted to remain high for several days.

Prevalence

Primary angle-closure glaucoma represents about 10 to 20 percent of all glaucomas. It is generally felt to occur more often in females, although in Negroes the sex incidence is approximately equal. Like primary open-angle glaucoma, it occurs predominantly in people over the age of 50, but it can be present at any age.

Heredity

Primary angle-closure glaucoma is a hereditary disease in the sense that anterior chamber depth and angle configuration are genetically determined. Thus, the anatomic predisposition to angle closure is inherited. It is only in such eyes that the events discussed above can lead to actual angle closure and pressure elevation.

It is of interest that the prevalence of nontasters of phenylthiocarbamide (PTC) is significantly lower among patients with proved angle-closure glaucoma than among nonglaucomatous populations and patients with primary open-angle glaucoma (*59*). The significance of this association is not known.

Diagnosis

The patient who presents with the classical symptoms of an acute attack of glaucoma along with gonioscopic evidence of angle closure usually is readily diagnosed. But since severe damage to both outflow channels and the optic nerve can develop rapidly during an acute attack, it is of considerable importance to identify these patients before such an attack occurs. The most important single factor in discovering patients with potential angle closure is the recognition of the shallow-chambered eye on routine eye examination. In most instances, this is easily done by flashlight or slit-lamp examination. Gonioscopy in these cases usually confirms the presence of a narrow angle. If, when the intraocular pressure is elevated in such an eye, the angle is partially occluded, and if the patient has had symptoms compatible with intermittent angle closure, the diagnosis is established. Even without pressure elevation or symptoms, however, any eye with a narrow angle should be investigated for its capacity to occlude. Since angle closure can often be induced by pupillary dilatation, this is used as a provocative test in suspicious eyes (*81, 83*). A pressure rise of 8 mm. Hg or more associated with gonioscopic evidence of angle closure after dilatation is considered a positive test. Mydriasis may be induced by keeping the patient in a darkened room for 60 to 90 minutes or by instilling a weak mydriatic, such as 5 percent eucatropine. Approximately 50 percent of eyes with the proven capability of angle closure will have a positive provocative test as defined above. Many more such eyes, however, will demonstrate a considerable reduction in outflow facility by tonography when dilated, without a marked pressure elevation. Thus, about 85 percent of eyes with proved angle-closure glaucoma can be identified by either a pressure rise or a reduction in outflow facility of 25 to 30 percent, associated with gonioscopic evidence of angle closure.

Unfortunately, a negative mydriatic provocative test does not rule out the possibility of angle closure in the future. A positive test in an eye with a narrow angle is of considerable help in diagnosis; a negative test is of less importance.

Therapy

With very rare exceptions, primary angle-closure glaucoma is a surgical disease, and medical therapy is useful only as a prelude to surgery (*81, 83, 85, 86*). Iridectomy is the procedure of choice. This permits a bypass for aqueous flow into the anterior chamber, eliminates the pupillary block, and permits the peripheral iris to fall back away from the angle structures. In contrast to primary open-angle glaucoma, patients with primary angle closure can often be completely cured of their disease by proper treatment performed early. Since the basic pathophysiology of pupillary block and angle closure usually exists in both eyes, it is advisable to perform bilateral iridectomies (*80, 84, 87*).

In one study, 89 percent of eyes whose fellow eyes had previously suffered an acute attack of angle closure themselves developed angle closure within 5 years when not treated (*87*). Even when treated with miotics, almost 50 percent developed acute attacks.

Medical therapy for primary angle-closure glaucoma is aimed at breaking the acute attack and normalizing the intraocular pressure so that surgery can be safely performed (*81*). The agents used are miotics, secretory inhibitors, and osmotic agents. Miotics act by pulling the peripheral iris away from the trabecular surface, permitting aqueous to reach the outflow channels. By making the pupil small, miotics

paradoxically aggravate the pupillary block mechanism, and intense miosis such as produced with cholinesterase inhibitors may provoke an attack. For this reason, Pilocarpine or Carcholin are the miotics of choice. In an eye with a high pressure, the sphincter muscle is often paralyzed and will not react to miotics until pressure has been lowered by other measures. Diamox is the secretory inhibitor most often used for this purpose and can be administered intravenously for more rapid effect. It has recently been noted that the systemic administration of hyperosmotic agents lowers intraocular pressure rapidly and dramatically. Intravenous urea and mannitol and oral glycerol are the agents most often used; they promptly lower intraocular pressure even with a completely occluded angle. Two other substances presently being investigated, orally administered isosorbide and intravenous ascorbic acid, appear to be equally effective and may offer several advantages over the other compounds.

After the acute attack has been broken and iridectomy performed, the eye with primary angle-closure glaucoma must be reevaluated. The pupillary block mechanism is eliminated by the surgery; but damage to the trabecular outflow channels during the period of angle closure may cause impaired outflow facility and increased intraocular pressure. Such eyes are managed like eyes with open-angle glaucoma.

Chronic Angle Closure (*81, 83*)

In some narrow-angled eyes, there may never be a sudden, total angle occlusion. Instead, there is a gradual increase in the area of contact between the iris and the meshwork. When there is closure of about two-thirds of the angle, a progressive rise in pressure begins and can slowly progress to 40 to 60 mm. Hg without associated symptoms of pain, haloes, or congestion. Over a period of years, these eyes gradually develop cupped discs and progressive field loss. Thus, it is possible to have a picture indistinguishable from that of primary open-angle glaucoma, except for the presence of gonioscopically occluded angles. In some of these eyes, iridectomy alone normalizes the pressure. More often, permanent synechias exist between the iris and trabecular meshwork, and additional miotic therapy or filtering surgery is necessary.

Plateau Iris

While most eyes with primary angle-closure glaucoma have shallow anterior chambers, an occasional eye with a deep anterior chamber will develop an acute attack of angle closure when the pupil is dilated. In these eyes, the iris is inserted on the ciliary body farther forward than usual, creating a narrow angle entrance. Pupillary dilatation bunches up the iris peripherally and presses it against the trabecular meshwork, triggering an attack of angle closure. In this very rare condition, pupillary block plays a minor role in the pathogenesis. Nevertheless, iridectomy is the procedure of choice, since any element of pupillary block aggravates the basic anatomic abnormality. The angle is usually opened slightly by this procedure, but miotics are still necessary to prevent future attacks.

PROBLEMS

More is known about the mechanism of primary angle-closure glaucoma than about most other types of glaucoma. Nevertheless, many questions remain to be answered.

Better methods of recognizing the patient with potential angle closure, and improved provocative tests are required so that patients prone to this disease can be discovered before an acute attack develops. Present provocative tests are positive in a high percentage of eyes with the proven potential for angle closure. Unfortunately, a negative test does not rule out the possibility of later occlusion of the angle, and too many eyes with negative provocative tests later develop acute attacks.

Careful studies of the hereditary aspects of angle structure and angle closure are needed. Why do some exceedingly narrow angles never occlude? What are the factors that contribute to or precipitate the occlusion?

While present methods of identification are not perfect, many patients could be saved the suffering and damage of an acute attack if they or their family physicians were better informed and able to recognize the signs and symptoms of the disease. Educational efforts should be made to teach physicians to recognize eyes with shallow anterior chambers. Physicians and their patients should be informed about the symptoms of angle closure and the value of prophylactic treatment in preventing acute attacks.

Some eyes that have suffered intermittent bouts of angle closure develop damage to outflow channels which persists following iridectomy and is not due to gonioscopically visible synechias. Other eyes with equally severe primary angle closure are completely normalized following surgery that eliminates the pupillary block. The nature of this secondary damage to outflow channels requires further investigation with careful clinical, anatomic, electron microscopic, and histochemical studies. If intraocular pressure can be restored to normal levels, is the secondary damage gradually repaired? If so, what steps (metabolic, etc.) are involved in the reparative process, and is the failure to repair the damage a genetic characteristic?

It has been suggested by some observers that visual loss in open-angle glaucoma occurs only when some abnormality in the optic nerve, genetic or metabolic, is present along with elevation of intraocular pressure. Careful study of eyes with damage from primary angle-closure glaucoma might demonstrate differences between pure pressure damage and damage related to a genetic or metabolic defect.

Present concepts suggest that glaucomatous field loss and cupping are the result of elevated intraocular pressure. Studies in patients with primary open-angle glaucoma have demonstrated that almost all eyes with field loss from this disease respond to topical steroids with a rise in intraocular pressure. This might suggest that glaucomatous-type field loss is genetically related to steroid responsiveness, but not necessarily due to elevated intraocular pressure. Eyes with angle-closure and secondary glaucoma offer an opportunity to check this hypothesis. About one-third of such eyes show a significant response when tested with topical steroids. If steroid response and field loss are genetically related, then only those eyes with angle-closure and secondary glaucoma that respond to steroids should develop field loss. If, however, eyes not responsive to steroids also show characteristic field changes, support would be given to the hypothesis that elevated intraocular pressure, from whatever cause, is the major factor in producing optic-nerve damage.

It is possible that the anatomic changes seen in the trabecular meshwork of eyes with primary open-angle glaucoma are the result of a genetically determined metabolic error or deficiency. This factor might also explain the steroid responsiveness of such eyes. Hopefully, this factor may be identifiable by immunologic or biochemical techniques. If such a metabolic abnormality is found, the question will arise whether the abnormal findings are a cause of, or a result of, the increased intraocular pressure of glaucoma. In other words, does pressure produce the change, or does the change lead to elevated pressure? Eyes with secondary glaucoma or angle-closure glaucoma provide an opportunity to answer such questions. Only about one-third of such eyes respond to topical steroids. If the metabolic abnormality is absent in those eyes that fail to respond to steroids, evidence would be obtained that such an abnormality was the cause of, and not the result of, elevated intraocular pressure.

The use of hyperosmotic agents has been one of the major recent advances in the treatment of acute attacks of angle-closure glaucoma. Better understanding of the details of action of these agents and their side effects is needed. The development of new drugs which avoid some of the hazards and disadvantages of the currently used agents should be encouraged. There is a special need for oral hyperosmotic drugs which are excreted quantitatively and do not enter into metabolic pathways.

INFANTILE GLAUCOMA
(*88, 89, 92, 94, 96, 98, 99*)

Infantile, or primary congenital, glaucoma is characterized by developmental anomalies of the anterior chamber angle of the eye, resulting in impairment of outflow and elevated intraocular pressure. The peripheral iris, instead of inserting on the ciliary body, runs directly into the inner trabecular meshwork in front of the scleral spur. Embryologically this represents failure of cleavage of the angle (*89, 94, 95, 99*). The scleral spur is poorly developed, and the meridional fibers of the ciliary body insert anterior to rather than on the spur. The inner trabecular sheets appear to sweep past the scleral spur to insert into the ciliary body. Whether the impairment of outflow is due to the abnormal pull of the meridional fibers of the ciliary body closing the trabecular sheets or due to the impermeability of these sheets or the tissue in front of them is not certain.

Due to obstruction of aqueous outflow from the eye, the intraocular pressure becomes elevated, usually in the range of 30 to 40 mm. Hg. Corneal epithelial edema develops, increasing and decreasing with changes in pressure. Epiphora, photophobia, and blepharospasm occur, probably related to the irritation of the corneal edema. Because of the relative elasticity of the infant eye, progressive enlargement of the globe develops when the intraocular pressure remains elevated. The corneal diameter increases, and tears develop in the less elastic Descemet's membrane. Cupping and atrophy of the optic discs may not be marked when the disease is first discovered, but they develop unless intraocular pressure is controlled.

Prevalence

Infantile glaucoma is a rare disease; the average ophthalmologist may see only one new case in 5 years of practice, and the disease represents only about 0.1 percent of patients seen in large eye clinics. In spite of the rarity, however, it is sufficiently common and devastating to be one of the more frequent conditions encountered at schools for the blind.

Over half of the cases are diagnosed within the first 3 months of life, often at birth, and the vast majority of cases (80 to 90 percent) are diagnosed by 1 year of age (*89, 92, 96*).

Heredity

The angle anomaly that reults in primary infantile glaucoma is genetically determined and exhibits a recessive inheritance pattern in most cases (*89*).

While the normal parents of patients with infantile glaucoma are carriers of the disease, topical corticosteroids do not identify the carrier state. This is unlike the situation in primary open-angle glaucoma.

Although sex linkage is not common in the inheritance pattern, about 65 percent of patients with infantile glaucoma are boys. The disease is bilateral in 75 percent of the cases.

Diagnosis

The most common early symptoms of infantile glaucoma are photophobia and tearing. It is usually the development of corneal haziness from edema, however, that brings the babies to the doctor. Occasionally the globe enlarges progressively without the development of corneal edema, and the child is seen by the ophthalmologist because of a large cornea.

Intraocular pressure, which can be reliably measured in infants only under deep anesthesia, is usually over 30 mm. Hg in infantile glaucoma. The pressure tends to be variable, however, and may not be elevated on all occasions. Hypotony occurs, especially shortly after a tear in Descemet's membrane. Tonography usually demonstrates outflow impairment below 0.15 (*92*). Gonioscopy reveals a wide angle recess with a flat insertion of iris into the trabecular meshwork. The peripheral iris and its radial blood vessels lift slightly at their juncture with the trabecular meshwork and often appear to be tented up toward Schwalbe's line by a semitransparent tissue membrane. Ophthalmoscopy and gonioscopy may be difficult if the cornea is edematous, but removal of the epithelium usually permits adequate examination.

The finding of an enlarged cornea with tears in Descemet's membrane, elevated pressure and impaired outflow facility, and typical gonioscopic appearance of the angle establish the diagnosis. Megalocornea, a condition of abnormal corneal enlargement but without glaucoma, can occasionally present difficulties in differential diagnosis. The absence of the other findings mentioned above usually makes accurate diagnosis possible. Metabolic diseases (Hurler's disease, corneal lipoidosis, cystinosis), trauma, rubella keratitis, and iridocyclitis can cause corneal haze and must be kept in mind. Similarly, trauma and intraocular neoplasms can cause secondary glaucoma with corneal enlargement and edema.

Therapy

Infantile glaucoma is essentially a surgical problem (*89, 92, 96, 98, 99*). Medical therapy is useful primarily to reduce the tension and clear the cornea so that surgery may be more accurately performed. Carbonic anhydrase inhibitors, like Diamox in doses of 5 to 10 mgm./kg. of body weight every 6 hours, are well tolerated and cause significant lowering of intraocular pressure.

One of the major surgical advances during the last two decades has been the development of goniotomy as the treatment for infantile glaucoma (*89, 90, 91*). It has proved to be the best procedure for this condition, with relatively little risk and generally gratifying results. Success seems to be the result of opening a route for aqueous flow into Schlemm's canal by means of a partial or complete trabeculotomy. It is not yet known whether this is due to incising an impermeable membrane, lowering the point of iris insertion on the trabecular meshwork, or interrupting an abnormal pull of the ciliary muscle on the trabecular fibers. A successful goniotomy increases the facility of aqueous outflow and normalizes intraocular pressure. The procedure is usually performed in about one-third of the angle circumference, and may be repeated in other areas if the initial operation does not sufficiently lower the pressure. External filtering procedures are usually not successful. Goniopuncture, whereby an opening is made to the subconjunctival space at the time goniotomy is performed, has been advanced by some surgeons (*97*).

Prognosis

Occasional spontaneous remission occurs, but most infants with infantile glaucoma go blind unless successful surgery is performed. If pressure is elevated and the cornea enlarged and hazy at birth, the prognosis is poor even with surgical intervention. Less than half of these eyes can be salvaged. When the disease does not become manifest until 2 months of age or older, over 80 percent of the cases can be arrested and intraocular pressure normalized by one or more goniotomies (*89, 92, 96*). Delay in treatment leads to corneal enlargement and decreases the probability of success. Even with normalization of pressure, however, special effort is necessary to prevent loss of vision from amblyopia in unilateral cases.

Glaucoma Associated With Congenital Anomalies (*92, 93, 98*)

Several congenital conditions are often associated with anomalies of the anterior segment of the eye and glaucoma. These anomalies are usually present at birth and constitute a small percentage of the cases of infantile glaucoma. Occasionally the glaucoma does not become manifest until later in childhood or early adult hood. Among these conditions are aniridia, Sturge-Weber syndrome, neurofibromatosis, Marfan's syndrome, Pierre-Robin syndrome, homocystinuria, Rieger's anomaly of mesodermal

dysgenesis, Lowe's syndrome, microcornea, and spherophakia. Glaucoma may also result from intraocular tumors in infants.

PROBLEMS

It is generally agreed that the developmental anomalies of the anterior chamber angle of the eye are responsible for infantile glaucoma. The exact nature of these anomalies, and especially the manner in which obstruction to aqueous outflow occurs, are uncertain. Additional histologic studies and careful electron microscopic studies are required. An impermeable endothelial layer lying over the trabecular meshwork has been described by some observers. Careful electron microscopic studies should be able to verify the existence of such a membrane, if it is present, or offer new explanations for the mechanism of this disease. Histochemical techniques for identification of the angle abnormality and better in vivo methods should be sought. Few electron microscopic descriptions of the angle structures in normal infant eyes are available, and additional studies are needed.

As judged by steriod testing of parents of children with infantile glaucoma, the genetic abnormality in this disease is different from that of primary open-angle glaucoma. Additional steriod studies are needed to verify this finding. Also, steroid testing of eyes with infantile glaucoma should be done.

Recent reports suggest that rubella may be much more important than previously thought in many ocular developmental diseases. The roles of this and other viruses as etiologic factors in infantile glaucoma should be investigated. Rubella keratitis has been described as a cause of corneal cloudiness even when not associated with infantile glaucoma. The differential diagnosis of these conditions can be quite difficult, and better diagnostic criteria are needed.

Few studies have been performed to establish values for intraocular pressure and outflow facility in normal infant eyes. If these parameters are to be intelligently used in the management of eyes with infantile glaucoma, better information on normal eyes must be obtained. This will require rigid standardization of depth of anesthesia and the use of applanation tonometers in the horizontal position.

New, controlled studies of the effects of various anesthetic agents on intraocular pressure and outflow facility are needed. Since deep anesthesia is required to obtain pressure-outflow values in infants, the effects of anesthetic agents may be of considerable importance in the management of children with the disease.

While the delineation of the anatomic abnormalities of infantile glaucoma requires additional histologic study, the mechanism of action of the surgery used to correct these abnormalities is in equal need of such study. Goniotomy has been used for about 20 years and has proven to be an effective surgical procedure. However, few followup studies have been made of eyes that have had successful goniotomies. Careful tonographic, gonioscopic, and histologic evaluation of these eyes would be of considerable value in determining the mechanism of action of goniotomy.

While presently used surgical methods are successful in most eyes with infantile glaucoma, many eyes are not controlled and continue to show progressive damage. There is good reason to suggest that the failure of some surgical procedures may be as much related to the scarring and damage produced by the surgery as to the disease itself. Present surgical techniques are far too gross, to perform accurately, a procedure that may be so delicate that it requires the incision of a membrane one cell-layer thick. New methods of carefully controlled microsurgery are needed, with visualization of the angle structures in high magnification and perhaps even with motor-driven stereotactic instruments that can be accurately positioned. It is only with such techniques that the surgical procedures can be accurately defined and their mechanisms of action more accurately studied.

Infantile glaucoma often goes undetected in the early stages of the disease because parents and pediatricians are unaware of the significance of the early symptoms. There is a constant need for better programs of education to inform pediatricians and general practitioners about infantile glaucoma. Any child with excessive tearing, photophobia, blepharospasm, or large corneal diameters should be referred to an ophthalmologist. When such children are seen early, proper management has an excellent chance of preserving vision. Delay, even for a month or two, can reduce or eliminate this chance.

Also, pediatricians should be altered to the frequent association of glaucoma with Sturge-Weber disease and neurofibromatosis. All children with these conditions should be carefully evaluated for glaucoma.

Certain congenital metabolic diseases are often associated with anomalies of the chamber angle and infantile glaucoma. Increased knowledge of the metabolic defects in such diseases as homocystinuria, Lowe's syndrome, and Marfan's disease may provide valuable clues to the biochemical regulation of cleavage and development of the angle structures.

SECONDARY GLAUCOMAS

(100, 104, 109)

Secondary glaucomas occur in conjunction with some other recognizable ocular disease which causes pressure elevation in the eye. In contrast to the bi-

laterality of the primary glaucomas, secondary glaucomas are often unilateral. Like the primary glaucomas, however, the pressure elevation may be due to visible obstruction of the angle, or the angle may be gonioscopically open.

Glaucoma Secondary to Inflammation

Inflammation of the anterior segment of the eye is one of the major causes of secondary glaucoma (*104*). During the course of anterior uveitis, the trabecular meshwork may become obstructed by inflammatory debris and keratitic precipitates, thus reducing outflow facility. Outflow may be further impaired by increased viscosity of the aqueous humor and by involvement of the trabecular meshwork by the inflammatory process. Since inflammation of the iris and ciliary body is usually associated with a decrease in aqueous secretion, intraocular pressure is usually not elevated in the acute phases of iridocyclitis, in spite of the impaired outflow facility. As the ciliary body recovers from the disease and aqueous secretion is restored, elevation of intraocular pressure may develop unless outflow facility recovers proportionately. Scarring of the trabecular meshwork may result in permanent outflow impairment and secondary open-angle glaucoma.

In the majority of eyes with iritis, no peripheral anterior synechias are found. In some cases of chronic iritis, however, the inflammatory process causes transudation from the capillaries and the formation of exudates in the angle recess. As these exudates organize and shrink, the iris may be pulled up toward the cornea, forming synechias which occlude the trabecular meshwork and impair outflow facility. When the inflammation is unusually severe, the iris may adhere to the lens near the pupil. If adhesions involve the entire circumference of the pupil, the aqueous is unable to get into the anterior chamber, and the iris is ballooned forward. The peripheral iris may be pushed against the trabecular meshwork, causing occlusion of the angle. This may result in acute angle-closure glaucoma. More often, aqueous secretion is so reduced by the inflammatory process that the pressure is low until the inflammation begins to subside.

Treatment of the above types of secondary glaucoma is aimed first at reducing the primary inflammatory disease, usually with corticosteroids. Where pupillary block is present, strong mydriatics are necessary to break the iris-lenticular adhesions. Occasionally a peripheral iridectomy is required to establish aqueous communication with the anterior chamber. The glaucoma itself is treated by agents which maximize the outflow through the residual parts of the angle still capable of functioning and by secretory inhibitors. Occasionally osmotic agents are necessary when an acute pressure elevation occurs.

Glaucomatocyclitic crisis is a reasonably discrete entity falling into this category of secondary glaucoma (*100*). Characterized by minimal inflammatory signs and symptoms and by open angles with elevated pressure and reduced outflow facility, it almost never results in synechia formation. The inflammatory disease may be confined entirely to the trabecular meshwork, with only occasional cells and flare in the anterior chamber and a few small discrete keratitic precipitates. The major complaint may be blurring of vision due to corneal edema. The process is usually unilateral, with recurrent involvement of the same eye. In contrast to the small pupil of anterior uveitis, eyes with glaucomatocyclitic crises have a dilated pupil. The attack rarely lasts more than 2 weeks, and both pressure and outflow facility usually return to normal values. Visual field changes are unusual. The attacks are best treated with mild mydriatics, topical corticosteroids, topical epinephrine, and systemic carbonic anhydrase inhibitors.

Corticosteroid-Induced Glaucoma

The use of corticosteroids to reduce inflammatory disease may, in itself, induce glaucoma (*47, 58*). It may occur in the presence of an open or an obstructed angle. As noted in the discussion of the heredity of primary open-angle glaucoma, approximately one-third of the normal population has the capacity to respond to topical corticosteroids with pressure elevation. This effect is the major cause of secondary glaucoma in many patients with inflammatory disease of the eye when the corticosteroids are used for prolonged periods. Fortunately, most inflammatory conditions respond to corticosteroids before the time required to produce pressure elevation. Many patients with corticosteroid glaucoma have used the medication for relief of chronic allergic conjunctivitis or blepharitis. In these patients, the disease closely resembles primary open-angle glaucoma in mechanism (reduced outflow facility), damage to the optic nerve, and response to therapy. Discontinuing the corticosteroids may improve or completely normalize the intraocular pressure and outflow facility. Unfortunately, the visual field loss is permanent. A major research effort is being made to develop corticosteroids which are effective anti-inflammatory agents but which do not induce glaucoma.

Neovascular Glaucoma

Neovascular glaucoma results from growth of fibrovascular tissue over the surface of the iris and trabecular meshwork (rubeosis iridis) (*104*). This re-

sults in marked outflow impairment and pressure elevation, often associated with recurrent hyphemas. The neovascular tissue usually leads to angle closure from peripheral anterior synechias. Rubeosis iridis is most commonly seen in diabetic retinopathy and following occlusion of the central retinal vein. It is also seen in some cases of central retinal artery occlusion, malignant melanoma, retinal detachment, arteriovenous aneurysms, carotid artery occlusion disease, Eales' disease, and Coats' disease. The rubeosis of diabetic retinopathy is almost always associated with retinitis proliferans and recurrent vitreous hemorrhages. When rubeosis iridis follows central retinal artery or vein occlusion, there is often preexisting primary open-angle glaucoma. This is important to recognize for the sake of the contralateral eye.

The etiology of the neovascularization in all of these conditions is completely unknown. It has been suggested that the relative retinal anoxia associated with most of the diseases in some way stimulates neovascularization. Why this should occur on the iris and trabecular surfaces has not been explained.

The neovascular glaucomas respond poorly to all forms of therapy, medical or surgical, and most of these eyes are lost, either from the underlying condition or the secondary glaucoma. Some few can be saved by filtering surgery performed with cautery and diathermy to coagulate the vessels. Recently it has been found that the rubeoisis temporarily regresses after cyclocryotherapy, allowing an interval in which surgery can be performed.

Glaucoma Secondary to Trauma

Trauma accounts for a large percentage of the secondary glaucomas. In penetrating injuries, the resulting glaucoma is dependent upon the position and extent of the injury, the skill with which the injury is repaired, and the posttraumatic inflammatory reaction of the eye. Blunt injuries are more common and may damage the eye in several ways. A blunt blow to the eye causes a sudden rise in intraocular pressure. The iris is pushed against the lens with tremendous force, and aqueous is unable to pass posteriorly through the pupil. The iris may tear in its thinnest portion in the periphery, producing an iridodialysis. In more severe cases, the tear may extend back into the ciliary body, producing a recessed angle, often accompanied by anterior chamber hemorrhage (*101, 113*). The hemorrhage may be large enough to block the outflow channels, resulting in a rise in intraocular pressure. Even when the bleeding is less massive, breakdown products of the blood may result in permanent damage to the outflow channels (hemosiderosis). Usually the initial bleeding is not extensive, and the blood resorbs rapidly. In a small percentage of cases, recurrence of hemorrhage occurs, most often on the second to fifth days, and is often accompanied by increased intraocular pressure. If the pressure cannot be lowered by secretory inhibitors and osmotic agents, the blood must be washed out of the anterior chamber to prevent bloodstaining of the cornea and damage to the optic nerve.

Angle recession is found frequently after traumatic hyphemas. An incidence of 71 percent was reported in one series (*101*). In a small percentage of these cases, probably under 10 percent, secondary glaucoma occurs. This glaucoma may develop within 2 months to a year after the recission and may be transient in nature. It is probably related to trabecular damage at the time of the injury. The reduced outflow is compensated for initially by hyposecretion of aqueous. As the ciliary body begins to function again, the glaucoma becomes manifest. If the trabecular damage is repaired and outflow restored, the pressure may return to normal levels. In other eyes, the glaucoma may not occur until 10 or more years after the original injury, producing a unilateral open-angle glaucoma. Gonioscopic evidence of a recessed angle and a history of blunt trauma are important diagnostic points in these cases. The condition is treated like primary open-angle glaucoma.

Intraocular foreign bodies, particularly those that contain iron, produce considerable damage to the eye (siderosis). The damage involves the lens, pars plana, retina, and trabecular meshwork. Changes in the trabecular meshwork closely resemble those seen in primary open-angle glaucoma. The resulting glaucoma is often difficult to control and persists even after the foreign body is removed. The treatment should be that of any other open-angle glaucoma.

Lens-Induced Glaucomas

The lens plays an important part in many of the secondary glaucomas. A swollen lens may shallow the anterior chamber, cause pupillary block, and result in an acute attack of angle-closure glaucoma. Removal of the lens after lowering the intraocular pressure cures the glaucoma if trabecular damage or peripheral anterior synechias have not occurred.

Traumatic or spontaneous subluxation of the lens can result in glaucoma with angle closure due to pupillary block by vitreous or the lens (*103, 106*). In many instances of lens subluxation, the outflow facility is decreased without angle closure. This is particularly true in Marfan's syndrome, where congenital angle anomalies may explain the glaucoma. In traumatic dislocations, angle recession is frequently found. In these instances the outflow impairment is probably related to the trauma rather than to the dislocated lens itself.

In phacolytic glaucoma, leakage of lens material

through the lens capsule and into the anterior chamber occurs. Macrophages containing lens material fill the angle and block the trabecular meshwork, producing elevation of intraocular pressure. Removal of the lens usually results in restoration of normal outflow facility and intraocular pressure. Recently it has been found that 25 percent of eyes with phacolytic glaucoma coming to pathologic examination have recessed angles (*108*).

Lens-induced uveitis results from reaction to lens material, either through the intact capsule or after rupture or extracapsular extraction of a mature cataract. The process is characterized by marked exudation of lymphocytes and plasma cells, invasion of the lens by leukocytes, much reaction in the anterior chamber, and conglomerate precipitates on the back of the cornea. The eyes are often soft during the acute reaction, but glaucoma may occur as a consequence of synechias and scarring. Cataract extraction or removal of cortical material cures the uveitis and alleviates or avoids the glaucoma.

Aphakic Glaucoma

Glaucoma in aphakic eyes may occur in the immediate postoperative period or many months after the surgical procedure. It may be the result of an underlying primary open-angle glaucoma or, more often, due to operative complications.

One of the serious complications of lens extraction is the formation of posterior synechias to the vitreous face or to the posterior capsule in extracapsular extractions. This creates a pupillary block and results in forward displacement of the peripheral iris. The anterior chamber may become completely flat, or may be filled centrally with a mushroom of vitreous but have peripheral angle closure. Aqueous humor is trapped in the vitreous and cannot reach the anterior chamber (*103, 107*). The symptoms may be similar to acute or chronic-angle closure glaucoma, depending on the rapidity and height of the pressure rise and the ability of the eye to compensate for that rise without becoming congested. An incomplete pupillary block can be present for a considerable time without becoming clinically manifest, particularly if the rate of aqueous production is so low that it does not overbalance the poor outflow. Treatment consists of relieving the pupillary block, either by breaking the posterior synechias with mydriatics or by performing an iridectomy. If extensive peripheral anterior synechias have formed, further medical or surgical therapy may be necessary to treat the impaired outflow and elevated pressure.

A second, and more frequent, cause of anterior chamber collapse following cataract surgery is leakage of the wound due to poor closure of the incision. The longer the anterior chamber is flat, the more probable it is that there will be a decrease in outflow facility due to permanent peripheral anterior synechias. A collapsed chamber present for 6 or 7 days should be reformed by air injection and drainage of subchoroidal fluid. When the anterior chamber remains flat for over 7 days, the incidence of glaucoma secondary to extensive peripheral anterior synechias is about 35 to 40 percent. When glaucoma occurs, the treatment is essentially the same as that of open-angle glaucoma, with emphasis on medical control, and resort to surgery only if medical therapy fails.

Epithelial ingrowth is a rare, but extremely serious, complication of cataract surgery. It may also follow perforating injuries to the eye and is almost always associated with a fistulous tract through the cornea. Epithelium enters through the tract and spreads over the back of the cornea and the anterior surface of the iris. Glaucoma results when the angle is sufficiently covered to obstruct outflow. This condition is extremely difficult to treat, and most of these eyes are lost. Occasionally epithelium can be removed with an alcohol sponge before the angle is compromised markedly, but not without considerable damage to the cornea. Epithelium introduced into the anterior chamber may also form cysts, rather than cover the entire chamber. Large cysts may impair outflow and result in glaucoma. The cysts are amenable to surgical excision or to obliteration by chemicals, diathermy, or photocoagulation.

Malignant Glaucoma

Malignant glaucoma is a rare surgical complication in which the anterior chamber either fails to form or collapses shortly after glaucoma surgery, and tension elevation recurs (*102*). The lens prolapses into the scleral ring, trapping aqueous behind it. Pupillary block then occurs, resulting in a flat anterior chamber and extremely high intraocular pressure. In almost all instances, this complication follows filtering operations on shallow-chambered, narrow-angled eyes. It is especially likely to occur if intraocular pressure cannot be normalized prior to surgery. Treatment consists of using strong mydriatics and cycloplegics (Atropine 4 percent and Neo-Synephrine 10 percent). The Atropine causes backward movement of the ciliary body away from the angle, tightening the zonular ligaments. This pulls the lens posteriorly away from the corneoscleral ring and may permit aqueous to reach the anterior chamber. The additional pupillary dilatation by the Neo-Synephrine also helps to relieve the pupillary block. When medical therapy fails, the most effective procedure is prompt lens removal.

Glaucoma Associated With Ocular Disease

There are a number of eye diseases that are frequently associated with open-angle glaucoma. In

these cases, the glaucoma is not truly secondary to the associated disease, but may share with it a common or related pathogenic factor. Among such diseases are:

1. High myopia.
2. Central retinal vein occlusion.
3. Retinal detachment.
4. Fuch's endothelial dystrophy.
5. Retinitis pigmentosa.

Two other conditions, pigmentary glaucoma and glaucoma associated with pseudoexfoliation of the lens capsule (*110, 111, 112*), have often been considered to be secondary glaucomas. While these glaucomas are rather well-defined clinical entities, there is serious question as to whether they should be classified apart from primary open-angle glaucoma.

PROBLEMS

The secondary glaucomas occur in conjunction with some recognizable ocular disease believed to be associated with or causative of the glaucoma. In some secondary glaucomas, the cause is obvious. In most cases, however, our knowledge of the mechanisms responsible for the glaucoma is extremely limited. Many of these conditions are suitable subjects for experimental studies, however.

The necessity of studying the mechanism of "steroid glaucoma" and its possible implications in the etiology of primary open-angle glaucoma have been discussed (sec. V). The anti-inflammatory properties of corticosteroids and their value in ophthalmology is unquestioned. The fact that such agents can produce glaucoma in susceptible eyes makes it necessary to find agents which maintain the anti-inflammatory properties without the pressure-raising properties. Efforts are needed to determine whether these properties *can* be dissociated. Since many diseases for which topical corticosteroids are used require only superficial anti-inflammatory agents (e.g., allergic conjunctivitis), it should be possible to develop additional agents that are superficially active but which do not penetrate the anterior chamber and affect the trabecular meshwork.

Intraocular inflammatory disease often causes a reduction in aqueous secretion. The mechanism of this reduced aqueous flow is unknown, as is the method of recovery with subsidence of the inflammation. Such studies can be performed in experimental animals and with tissue culture of ciliary epithelial cells. The necessary techniques are available and need only to be applied to this area. Biochemical alterations and their effects on ciliary body metabolism can be evaluated; histochemical and electron microscopic techniques are available. Knowledge of the ways of influencing the recovery process of aqueous secretion might prevent the development of glaucoma in patients with inflammatory disease.

Information is also needed on the mechanisms of repair of the trabecular meshwork following traumatic or inflammatory damage. Here again the tools for such study are currently available, including experimental animals (e.g., monkeys) whose eyes are similar to the human eye. The knowledge of such mechanisms and ways to alter the environment so as to obtain optimum conditions for recovery are of considerable clinical importance. Clues obtained in such experiments could also be applied to the study of primary open-angle glaucoma, and biochemical and enzymatic abnormalities or deficiencies searched for.

Similar investigations should be carried out in monkeys on the factors involved in hemolytic, or siderogenic, glaucoma. We know that anatomic changes in the trabecular meshwork occur in this condition, and it seems likely that the iron molecule in some way interferes with the metabolic pathways of the cells of the meshwork.

Glaucomatocyclitic crisis is a rare type of glaucoma associated with mild inflammation and occurs in repeated, self-limited bouts. Histologic and histochemical descriptions of the trabecular meshwork in such eyes have never been made. The fact that such marked outflow impairment can completely regress in a matter of only 2 weeks or less suggests that the cells of the trabecular meshwork possess considerable reparative properties.

Neovascular glaucoma presents many problems involving both etiology and therapy. Why retinal hypoxia or anoxia should stimulate neovascularization over the iris surface is not known. The elaboration of some vessel-stimulating "x" substance from hypoxic tissue has been postulated, but the nature of this substance is obscure. Efforts should be made to induce rubeosis in experimental animals, and biochemical studies should be made to find vessel-stimulating substances in hypoxic ocular tissues, especially retinal tissue. The rare occurrence of rubeosis iridis in eyes with choroidal malignant melanomas suggests that a product elaborated by the tumor is also able to stimulate neovascularization. Studies of such tumors might lead to the discovery of the substance. Therapy of neovascular glaucoma has been almost universally unsuccessful. More careful and thorough examination of patients susceptible to developing rubeosis (diabetes, central vein occlusion, etc.) has led to the discovery of neovascularization in the chamber angle of eyes before any pressure elevation or congestion develops. This neovascularization at times appears to arise from Schlemm's canal. In spite of early identification, no way to reverse the process is known. Such methods

are badly needed, as are ways of treating the full-blown picture when it develops.

Glaucoma in association with recession of the chamber angle in eyes that have suffered blunt trauma has recently been well documented as a clinical entity. The mechanisms responsible for the anatomic changes in the trabecular meshwork are not known. Obviously the damage is related to the trauma, but why complete functional repair occurs in some cases and not in others is not understood. Even more baffling is why the glaucoma in some of these eyes does not develop for 10 or more years following the trauma. Angle recession can be produced in experimental animals and histologic and biochemical studies performed at varying time intervals. Such studies might answer many of the present questions about this condition. Recent studies have shown that the opposite eyes of patients with traumatic recessions in one eye have a remarkably high percentage of steroid-responsiveness. Why steroid-responsive eyes should be more prone to develop angle recession with trauma is entirely unclear. Nevertheless, it appears that trauma is more likely to lead to glaucoma in eyes that respond to steroids with increased intraocular pressure.

Ideas about the relationship of lens dislocation to glaucoma have undergone considerable change in recent years. This has largely been due to the discovery of angle recessions in many of the eyes with glaucoma and dislocated lenses. This suggests that the subluxated lens per se is not the causative factor. Experimental studies are needed to demonstrate whether eyes with enzyme-induced lens dislocation are prone to develop glaucoma, and whether surgical removal of the lens alters the course.

"Enzymatic" glaucoma is another recently described entity which requires much further research (*105*). The frequent occurrence of elevations of intraocular pressure in the early postoperative period in eyes in which alpha-chymotrypsin was used for zonulysis has been well documented. The effect appears to be due to temporary damage to outflow channels, with complete recovery in about 2 weeks. Long-term studies of such eyes are needed, and the mechanism of damage and repair of the trabecular meshwork needs clarification. Detailed study of this condition must be done with complete histology, electron microscopy, biochemistry, and histochemistry, using laboratory animals, especially monkeys.

Additional work is need for better definition and treatment of the lens-induced glaucomas not associated with lens dislocation. Experimental production and study in laboratory animals is necessary.

Epithelial ingrowth, while much more rare than neovascular glaucoma, is equally as difficult to manage and almost always results in loss of the eye. Numerous attempts to induce this condition in laboratory animals have been unsuccessful. The lack of an experimental model has greatly hampered therapeutic efforts, and new attempts must be made to reproduce the condition in animal eyes. Only then will it be possible to evaluate reliably therapeutic measures such as X-ray and develop better methods of prevention and cure.

Another rare secondary glaucoma, malignant glaucoma, has been the subject of considerable speculation regarding mechanism and treatment. Present concepts require additional study and confirmation. Again, the rarity of the condition in human eyes necessitates renewed efforts to reproduce and study the disease in laboratory animals.

The relationship between glaucoma and high myopia is not understood and needs to be investigated. The fact that buphthalmos develops in infant eyes when intraocular pressure is elevated suggests that slight elevations of intraocular pressure might be important in the progressive enlargement of eyes with myopia. Steroid testing of otherwise normal myopic eyes should be performed to determine whether such eyes resemble those genetically susceptible to primary open-angle glaucoma. The possibility of preventing progressive myopia by lowering intraocular pressure in young myopes is intriguing. If steroid-responsive laboratory animals can be found, the possibility of producing ocular enlargement by moderate degrees of pressure elevation can be studied. Electron microscopic, histochemical, and biochemical studies of the trabecular meshwork in myopic eyes is needed.

The relationships between glaucoma and retinal detachment require further study. The mechanism whereby eyes on miotics tend to develop retinal tears needs investigation. Laboratory animals can be used to determine how and where ciliary-body contraction causes tension or strain on the choroid and retina. Common metabolic deficiencies or abnormalities in the choroid, retina, vitreous, and trabecular meshwork of eyes with glaucoma and eyes with retinal detachment should be searched for.

Metabolic studies of corneas of patients with endothelial dystrophy might provide clues to a possible metabolic abnormality of the endothelial cell related to a basic defect in primary open-angle glaucoma. Since corneal transplants are often performed on these patients, fresh human material for laboratory study is available.

The relationship between the pigment abnormality of Krukenberg spindles and the development of glaucoma is not known. The commonly held belief that mechanical pigmentary obstruction of the trabecular meshwork is the cause of the glaucoma in these patients has not been proven. The frequent occurrence of primary open-angle glaucoma in relatives of patients with pigmentary glaucoma should

be further emphasized. Steroid testing of nonglaucomatous patients with Krukenberg spindles should be continued. Similar comments and suggestions for study can be made about glaucoma and pseudoexfoliation of the lens capsule. Both of these conditions require additional histologic, electron microscopic, histochemical, and biochemical studies. They both may be clinical manifestations of a gene identical with or closely related to the one that determines intraocular pressure response to topical corticosteroids.

CONCLUSIONS

The seriousness of the problem of glaucoma is illustrated by the fact that almost one-seventh of all newly blind persons in this country are blind as the result of glaucoma. Numerous surveys have estimated that about 2 percent of the population over the age of 40 are victims of this disease. Recent genetic studies suggest that this figure may actually be about 4 percent—that is, about 4 percent of the total population may have the genetic predisposition to develop glaucoma. The disease often develops in individuals at the height of their earning capacity. Since it is initially symptomless in most cases, serious loss of vision may occur before the disease is discovered. The potential loss in earnings and general achievement, both to the individual and to his community, is enormous. The necessity of preventing such tragedies is obvious.

The term "glaucoma" actually refers to a group of diseases, all of which have in common an elevation of intraocular pressure. Such pressure elevations in susceptible eyes lead to atrophy of the optic nerve and loss of vision. The exact mechanism by which such damage develops is unknown. The factors which determine the susceptibility of the individual eye to pressure damage and how these factors may be altered to prevent such damage represent major areas for intensive investigation.

Carefully conducted epidemiologic studies are needed to improve our understanding of the early stages and the natural history of glaucoma. Again the aim is the identification of the earliest signs that indicate which patients are likely to lose vision, so that treatment can be substituted. Studies such as the Collaborative Glaucoma Study, designed to carefully follow "high risk" patients for periods of 20 to 30 years, may provide the answers to these basic questions.

Equally as important as recognizing the susceptible patient is understanding the mechanisms that control intraocular pressure and why variations in it occur. Better instrumentation for measuring the various parameters of intraocular pressure and the development of methods to study the factors that influence this pressure are required. Careful anatomic and physiologic studies of the eye are needed. Only when the normal regulatory mechanisms are better elucidated can the abnormal situation be understood. The development of strains of animals that develop spontaneous glaucoma that resembles human glaucoma would permit better study of the disease. Some success has been made in breeding a strain of glaucomatous rabbits. Further efforts are needed to continue this strain and develop others so that large numbers of animals may be available for study.

Periodic conferences of experts in many areas should be conducted to outline the best ways to approach and solve the problems of glaucoma. These conferences should include anatomists, electron microscopists, neurophysiologists, pathologists, biochemists, pharmacologists, geneticists, and clinicians. In this way the latest techniques and methods of study can be made available and applied to the understanding and control of glaucoma.

Recent studies of pressure response to topical corticosteroids have opened a new avenue to the genetic study of glaucoma. If present concepts prove correct, it may be possible to identify the "genetic glaucoma" patient many years before he actually develops the disease. Long-term studies of steroid-tested patients are required. The mechanism of the pressure response to corticosteroids needs intensive study. Efforts should be made to develop a strain of laboratory animals whose eyes respond in a manner similar to human eyes. Such efforts thus far have been unsuccessful. Additional investigations of the association of glaucoma with other genetically determined diseases should be encouraged.

The need for new therapeutic approaches to glaucoma is also great. All present therapy is directed toward lowering intraocular pressure. It is entirely conceivable that equally effective, and perhaps even superior, methods of therapy could be devised that would increase the resistance of the optic nerve to pressure damage. Here again, the normal metabolic functions of the optic nerve must be studied in greater detail so that ways to combat the abnormal situation can be developed.

Methods for evaluating new drugs and new approaches to treatment must be made available. Animal studies are needed, followed by carefully controlled investigation in glaucoma patients. Clinical research centers designed to follow and treat glaucoma patients and glaucoma suspects should be established. Such centers could incorporate laboratory as well as clinical studies under carefully controlled conditions with thoroughly evaluated patients. This would provide an ideal situation, permitting clinical problems to be taken to the laboratory for animal study, and allowing new research developments to

be brought to patients for carefully conducted evaluation. Both new medical and surgical improvements in the management of glaucoma could be studied in this fashion.

Most of the above recommendations involve the study of glaucoma in adults. Glaucoma also occurs in children, though fortunately much less often. Nevertheless, it can be equally as devastating in the destruction of vision, and it represents one of the most common conditions seen in schools for the blind. The disease is caused by abnormal development of the eye during the period before birth, although the condition may not become evident until a few months after birth. Careful studies are needed in many areas to improve the understanding and treatment of this type of glaucoma. These should include anatomic studies of glaucomatous eyes, evaluation of the role of rubella and other viral diseases as etiologic agents, better studies of intraocular pressure and the factors influencing pressure in normal infants and children, better evaluation of present surgical techniques of treatment, and the development of new, more effective therapeutic techniques. Equally important are better programs of education to inform pediatricians and general practitioners about infantile glaucoma and its early recognition.

The secondary glaucomas occur in conjunction with some recognizable ocular disease which leads to the pressure elevation. The causes of secondary glaucoma are numerous, and many are poorly understood. The relative rarity of some of these conditions makes this study very difficult. As a group, however, they represent some of the most severe and hard-to-manage glaucomas. Experimental production of these conditions in laboratory animals is a major need and should be strongly encouraged.

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Chapter 10—CATARACTS

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INTRODUCTION

A cataract is any opacity or clouding of the ocular lens; it is not a growth; and the cornea is not involved, as is sometimes believed. Opacity is caused largely by a change in the physicochemical state of the lens proteins and may vary from a few small spots to an area involving so much of the lens that almost total blindness results. Cataract may be evident at birth or not until the eighth or ninth decade of life; it may appear in any part of the lens, and may remain stationary or progress at varying rates until the lens becomes completely cloudy.

The lens has a higher protein content (ca. 35 percent) than any other tissue. The protein molecules are uniquely arranged so as to comprise a surprisingly transparent mass. Surrounding the lens is the capsule, a thin amorphous hyaline membrane beneath which, on the anterior side only, lies a single layer of cells known as the epithelium. The bulk of the lens consists of fibers which are formed from epithelial cells at the equator. As new fibers are produced they become displaced into the deeper parts of the lens where they lose their nuclei.

The outer part of the lens is called the cortex and the inner part the nucleus, the morphological distinction between them being the difference in the integrity of the fibers. The cell walls of the fibers become progressively less recognizable toward the center of the lens until in the nucleus the lens substance has a completely homogeneous structure.

Lens transparency depends upon many factors, most important of which is maintenance of a normal balance between soluble and insoluble proteins in their undenatured state. The proteins are distributed in cells and fibers which are arranged regularly throughout the organ. Any disturbance in this highly organized system may result in cataract formation. The most common variety is senile cataract, so called because it occurs most often in the eyes of persons past middle age. These cataracts appear to be a part of the general aging process in the human body.

The etiology of most varieties of cataract remains obscure, but the condition is frequently correlated with local or systemic disease processes. Cataracts are often connected with, or secondary to, ocular diseases such as uvetitis, aniridia, and retinitis pigmentosa and are evident in systemic diseases that involve disturbances in metabolism, frequently of an hereditary nature, such as galactosemia, diabetes, or myotonic dystrophy. They may occur in children born of mothers who had German measles during the first trimester of pregnancy. They may result from exposure to chemicals such as thallium, dinitrophenol, naphthalene, triparanol, and corticosteroids, or physical agents such as ionizing radiations like X-ray or gamma ray, neutrons, and beta particles, or from radiant energy of lower energy such as infrared and microwaves. Trauma from a blunt instrument or a perforating injury of the globe usually produces total opacification of the lens, although partial opacity in the path of the pentrating foreign body may develop.

STATISTICS

Senile cataract is the leading cause of legal blindness in the United States, and accounts for an estimated 15.6 percent of a total of about 400,000 blind persons. An additional 6.5 percent (25,000 persons) are blind because of cataracts with other etiologies:

	Percent
Congenital	3.4
Diabetes	1.4
Vascular disease	1.1
Other, including infections and trauma	.6
	6.5

Among new cases of blindness in 1962, senile cataract was responsible for 13.7 percent of the estimated 31,350 cases, and was second only to glaucoma (15.0 percent) as a cause of blindness. An additional 7.4 percent were due to other causes associated with cataracts: congenital 4.2 percent, diabetes 1.5 per-

cent, vascular 1.2 percent, and other, including infections and trauma, 0.5 percent.[1]

In Canada, cataract is also the major cause of blindness, accounting for 15 percent of the total 25,000 cases, 1,349 of which were congenital, 225 diabetic, and 198 traumatic.

Little is known about the epidemiology of senile cataract other than that there is some evidence that it occurs more often in patients with diabetes than in other individuals over the age of 50. Partial opacities of the lens must occur still more frequently. They could be responsible for a significant proportion of automobile accidents, especially those occurring at night where even slight opacity may give rise to a confusing image when viewing headlights.

TREATMENT

At present, surgery is the only effective therapy for cataracts once they have formed. In some cases prophylactic measures are helpful. Cataract formation can sometimes be prevented or delayed: In diabetics, by early diagnosis of the disease and control with insulin; in congenital galactosemia, by withdrawal of lactose or milk from the diet; in radiation cataracts, by proper shielding. Massive immunization or innoculation of females with rubella virus to produce immunity before reaching childbearing age, might reduce the number of infants born with cataract caused by rubella.

An important criterion for surgical removal of a cloudy lens is the amount of visual acuity needed by the patient for his daily activities. Procedures for surgical extraction of cataract have remained basically the same for the last 200 years, although many modifications for improved safety and effectiveness of the operation have been proposed since then. It is no longer thought necessary to wait for a cataract to mature before removing it.

Restoration of vision does not always accompany extraction of congenital cataracts because many of the important reflexes associated with normal visual acuity and binocular vision are not fully developed until several months after birth. A child born with dense cataracts in both eyes may never learn to fixate objects properly, and nystagmus may develop even though the cataracts are successfully removed. Moreover, eyes with congenital cataracts are predisposed to retinal detachment and to some diseases, such as glaucoma.

Surgical extraction of cataract does not always assure removal of a patient from a blind group, because complications, such as high myopia, trauma, macular degeneration, retinitis pigmentosa, and the retinopathies may develop.

[1] Source: National Society for Prevention of Blindness.

Some patients refuse surgery because of age, general health, or fear of losing total vision. Others refuse because their general practitioner does not recommend the operation, or they are content with their status as a blind person.

Devices commonly employed to correct the refractive error after removal of the lens are: (1) Spectacles containing highly corrected lenses, (2) contact lenses, and (3) a plastic lens inserted directly into the eye to replace the one removed. At present, however, artificial implants are not entirely satisfactory.

RESEARCH

Most disease-oriented research on the lens is concerned with discovering the chemical and physical changes associated with development of cataracts in eyes of experimental animals, since a fresh human lens that has not become completely opaque is rarely obtainable from an individual with a specific ocular disease.

Experimental cataracts can be produced by many unrelated methods, and it is not unexpected, therefore, that the mechanism by which clouding of the lens occurs is equally diverse. Some kinds of experimental cataracts have a clinical counterpart.

While it may be hazardous to extrapolate from observations made on experimental animals to an apparently similar disease entity in man, the risk is probably not as great in the case of the lens as in other organs, because of the many similarities in metabolism, antigenic properties and mode of growth of lenses from different species. Thus experimental cataracts probably are of value in assessing the mechanism of their formation in man.

Sugar Cataracts

Elevation of any aldose, glucose, galactose, or xylose in the blood and aqueous humor leads to the production of cataracts in experimental animals. Glucose levels are raised as a result of diabetes produced either by pancreatectomy or administration of alloxan; the concentration of galactose or xylose is increased by feeding animals diets rich in these sugars. Similarities in the appearance and histopathology of each kind of sugar cataract suggest that a common mechanism may initiate the cataractous process, the first pathologic sign of which is the appearance of hydropic lens fibers.

The mechanism of cataract formation involves conversion of large quantities of glucose, galactose, or xylose to their corresponding sugar alcohols, sorbitol, dulcitol, and xylitol, by the enzyme aldose reductase. The reaction depends on the availability of the cofactor triphosphopyridine nucleotide (TPNH). A marked decline in activity of the direct

oxidative pathway (hexosemonophosphate shunt) with the maturity of the lens is responsible, in large part, for the production of TPNH and accounts for the decreasing susceptibility of rats, with age, to the development of sugar cataracts.

The sugar alcohols which accumulate within the lens fibers because of the impermeability of the fiber membranes create a hypertonic condition. Osmotic equilibrium is reestablished by the passage of water into the lens fibers causing them to swell. The swelling continues until the lens fibers rupture, and disintegrate, leaving open spaces or clefts which cause clouding of the lens, first at the equator and finally throughout its whole substance.

Simultaneously there is a reduction in the rate at which glucose is metabolized via the hexose monophosphate shunt, and in the concentration of adenosince triphosphate (ATP). Breakdown of glucose through the glycolytic and citric acid cycles remains normal in the early stage of cataract. The concentration of most free amino acids also declines both because of impairment of the "pump" responsible for actively transporting them across the epithelium and because of an increase in the rate of leakage out of the lens across the capsule.

The rate of net synthesis of soluble proteins is decreased, perhaps because of lowered levels of free amino acids, although lack of ATP may also be responsible for slowing of protein synthesis. The concentration of albuminoid increases relatively, and, as in other forms of cataract, the levels of glutathione and coenzymes both decrease.

Eventually the concentration of the cold-precipitable protein fraction declines to about one-third the normal level after feeding galactose, but this does not occur until permanent opacification develops.

Radiation Cataracts

The mechanism of cataract formation has been studied extensively in animals following exposure to various forms of radiant energy. Irradiation of the lens is especially useful for studying cataract formation because it is the only method, except massage of the lens, whereby cataract can be produced in one lens of an animal while the other lens remains unaffected and serves as a control.

Many forms of radiation are known to produce cataracts; these include shorter diathermy waves, infrared rays which produce glassblowers' cataract, and ionizing radiations such as beta particles, neutrons, X-ray and gamma ray. Neutrons are the most damaging. While ultraviolet light does not damage the lens, because most of it is absorbed in the cornea, certain drugs, like methoxalen, used as a suntanning agent and for the treatment of vitiligo, and some tranquilizers, like phenothiazine, may act as photosensitizing agents and make otherwise harmless forms of ultraviolet radiation potentially cataractogenic.

1. *Ionizing Radiations.*—The lens, especially when young and rapidly growing, is particularly susceptible to ionizing radiations. A single dose of radiation above the threshold level induces irreversible changes which inevitably affect transparency of the lens. The lens becomes opaque only after a latent period of weeks or months, depending on the dose, after any inflammatory reactions have completely subsided. While both X-rays and neutrons cause nuclear damage to proliferating cells most of the evidence available suggests that heavily ionizing particles, like beta rays and neutrons, are more efficient in producing nuclear damage than X-rays or gamma rays. On the other hand, there is some reason to believe that X-rays are especially effective in inactivating enzymes, thereby interfering with metabolic processes. However, these effects are often reversible with time, so it is not surprising that experiments have shown neutrons to be more effective than X-rays in producing permanent lens damage. The degree of opacity and the latent period of development are inverse functions of both dose and age, the cataractogenic dose level for mice and rabbits lying between 100 and 250 R. for acute exposures, and the fast neutron dose level between 1 and 10 r.e.p. (roentgen equivalent, physical).

The peripheral portion of the lens epithelium is the primary site of damage which leads eventually to radiation cataract, the first appearance of which is seen clinically at the posterior pole. Irradiation of only the central portion of the lens with large doses of X-rays (400 R.) does not cause opacity.

Initiation of mitosis (cell division) of the epithelial cells of the lens is blocked immediately after radiation, followed by an overcompensating increase in mitotic activity. The number of cells capable of incorporating tritiated thymidine into deoxyribose nucleic acid (DNA) also decreases, but less abruptly than mitosis, suggesting that these processes may not be directly related. Both mitotic activity and the number of labeled nuclei return to normal level (following an overshoot), within several hours to 1 week, depending on the initial dose of radiation.

Some epithelial cells are killed by radiation, others undergo aberrant mitosis, whereby they become monster cells with abnormal cytoplasmic content and multiple nuclei. Whether these cells die or develop further is not known. Other cells are damaged by the radiation and become abnormal when they start to differentiate into lens fibers near the equator. These cells survive, and perhaps divide, but cease to form normal lens fibers. They remain globular and migrate or are pushed toward the posterior pole between the cortex and the capsule, where they form the characteristic opacity of early radiation cataract.

The inability of the lens to rid itself of abnormal, damaged or nonviable cells is a primary reason for its susceptability to chronic doses of radiation.

The earliest biochemical effect of X-rays in lenses of young rats is a marked increase in turnover of albuminoid ribonucleic acid (RNA). This phenomenon occurs within 3 hours after exposure, while microsomal and soluble RNA remain unchanged. The turnover of albuminoid RNA returns to relatively normal levels by the second or third week, at which time the initial changes in carbohydrate metabolism first become manifest. The concentration of lactic acid begins to decrease 3 to 4 weeks after irradiation, and a decline in the activity of glucose-6-phosphate dehydrogenase, as well as some of the glycolytic enzymes, becomes manifest shortly thereafter. A measurable loss in ATP can also be demonstrated 1 week after irradiation.

The level of glutathione decreases following X-radiation as it does in sugar cataracts. The enzymes which require sulfhydryl groups for activation decrease also, but only after the concentration of glutathione declines. The level of soluble protein in X-irradiated lenses slowly but progressively falls; however, the concentration of albuminoid protein increases 3 to 4 weeks after irradiation. These alterations in lens proteins following irradiation become more pronounced with time. The increase in albuminoid level, which is considered to be one of the parameters of the aging process in the lens, appears to be accelerated following exposure to ionizing radiation.

The possibility that RNA and DNA are affected early in lenses that develop cataracts as a result of ionizing radiations seems very likely. No early alterations occur in the electrophoretic behavior of proteins of irradiated lenses, but an 8-percent decrease in total protein takes place in partial X-ray cataract.

The injurious effects of shortwave radiations on tissues, at least in part, have been ascribed to the production of free radicals which have great chemical reactivity, particularly with compounds that contain sulphydryl groups, Based on this so-called indirect action theory of radiation damage, attempts have been made to protect cells against radiations by providing additional quantities of sulphydryl or other reducing compounds which may act as scavengers. Thus it was observed that intravenous administration of cysteine in rabbits prior to radiation provided a strong protective action against damage to the lens. Subsequent subconjunctival injections of cysteine at intervals after radiation did not reduce the number of fine opacities in the cortex, nor did pretreatment with cysteine by injection prevent inhibition of cell division, recovery, or compensatory increase in activity. Glutathione and thiourea were less effective than cysteine in increasing the resistance of the lens, as were other sulphur containing agents, and reducing compounds that did not contain sulphur. Inhibition of cell division and the compensatory increase of mitotic activity of the lens epithelium were not greatly affected by pretreatment of the radiated animals with cysteine.

2. *Microwave Radiations.*—Shortwave diathermy and microwaves of the kind used for radar-detection systems in commercial and military installations can produce cataracts in experimental animals, and there are cases known in man. Shorter waves produce cataracts in the posterior cortex directly beneath the lens capsule similar to those which result from exposure to ionizing radiations, but the latent period is very much less. Longer microwaves result in opacities in the anterior cortex resembling those caused by intense doses of infrared radiation.

The threshold for a single damaging exposure is determined by both the power density and the duration of exposure. In general, pulsed radiation with high-peak intensities is more potent in inducing lens opacities than continuous radiation. The effect of microwaves is cumulative and any intensity above a power density of 10 mW. per square centimeter must be considered potentially hazardous.

Microwaves elevate the temperature of the absorpent tissue, but opacity of the lens is not associated with any critical intraocular temperature. Heating of the eye may be only coincident with cataract formation and not its cause.

Biochemical studies on microwave-irradiated lenses have shown a reduction in the concentrations of glutathione and ascorbic acid. The effect on the level of ascorbic acid is unique to microwave-induced cataract.

There is no known treatment which can alter the progress of a cataract once it has developed. However, apart from the therapeutic application of diathermy, the risk in everyday life of exposure to damaging intensities of microwaves of 3 cm. wavelength, as used in radar, does not appear to be great. Protection could be afforded by covering the head with a close fitting mask of copper or bronze screen wire.

3. *Infrared Radiation.*—Absorption of sufficient infrared radiation can result in the immediate formation of a lens opacity accompanied by marked damage to the other tissues in the anterior segment of the eye. Frequent repetition of subacute intensities of infrared radiation in man produce a delayed opacity, sometimes appearing as much as 5 or 10 years later, starting at the outer layers of the posterior cortex, and often accompanied by splitting of the zonular lamellae in the pupillary aperture. The lesion, which in its final form is difficult to distinguish from ordinary senile cataract, is known as glassblowers' cataract. The cause of the cataract is

not known, but studies with rabbits suggest that it results indirectly from the heat absorbed by the iris and transmitted to the front surface of the lens, where it probably damages the epithelium. This mechanism of action would account for the long latent period preceding the opacity, but there is no explanation of how relatively slight increases in temperature adversely affect the metabolism of the epithelial cells.

Theoretically, all heat cataracts can be eliminated by wearing goggles made of glass that contains ferrous oxide which effectively absorbs infrared radiations. Excessive perspiration makes protective goggles uncomfortable, if not impractical, to wear near furnaces and ovens. Therefore, the best way to avoid heat cataracts is to reduce the intensity of radiant energy to safe limits of less than three calories per square centimeter per minute by means of screens that absorb or reflect much of the heat, or to automate the process so that the worker is not exposed to excessive radiant energy.

Nutritional Cataracts

Lack of a number of so-called essential amino acids in the diet of young rats results in cataract formation, presumably because the lens cannot synthesize protein normally. The net synthesis of soluble protein is arrested and growth of lenses of animals fed rations deficient in tryptophane, an essential amino acid, is inhibited significantly before the first cataractous changes develop.

Diets deficient in riboflavin (vitamin B_2) also cause cataracts in rats, and lack of vitamin E in the mother rat and of folic acid in turkeys produces cataract in the offspring. There is no clear-cut evidence that dietary deficiency to the point of starvation causes cataracts in man, although the possibility that the nature of the food eaten by the people of India may contribute to the high incidence of cataract in that country has not been disproved.

Hormonal and Toxic Cataracts

Most research on cataracts has been concerned with lesions produced by excessive sugar intake or exposure to radiations. However, certain hormones, or lack of them, as well as toxic agents, also cause lens opacities. Cataracts are found in patients with rheumatoid arthritis who are given corticosteroid hormones for extended periods. They are found also in individuals who have had their parathyroid glands removed, and in patients with other disorders which result in tetany. The pathogenesis of steroid cataracts is not known. However, the cause of cataracts that result from hypoparathyroidism and other tetany-producing conditions seems to be associated with reduction of the calcium level in the blood. Lowered calcium levels alter the permeability of the lens capsule, and more importantly, decrease the efficiency of the ion pumps in the epithelium which control the electrolyte (salt) and amino acid levels in the lens.

A variety of toxic substances and some drugs cause lens opacities in experimental animals, and in some instances, in human beings; these include thallium, naphthalene, dinitrophenol, iodoacetate, mimosine, myeleran, and triparanol. However, hardly anything is known about the underlying mechanisms by which these substances induce lens opacities or whether they have any relation to the etiology of senile cataract. Prevention can clearly be accomplished by avoiding them.

Senile Cataract

As the lens ages, fibers become more dense, lose their nuclei, and turn yellow. Insoluble protein (albuminoid) increases relative to the soluble proteins (and crystallin), and the rate of protein synthesis decreases progressively. Water and soluble proteins are slowly lost from the nucleus, although the protein retains its chemical identity. Why opacities begin to form in some of these aging, hardening lenses is unknown. Two main types of cataract occur: nuclear, or sclerotic, in which the dense nucleus becomes opaque; and cortical, the more common of the two, which is characterized by hydration and swelling of the cortex.

The nuclear or sclerotic form of senile cataract may represent the final stage of the aging process of the dense nucleus. Cortical cataract, however, is not related to other known metabolic changes associated with aging, but is characterized by hydration and swelling of the cortex.

Apart from the gross changes in the properties of some protein constituents of the lens, little is known about alterations in the chemical composition of human senile lenses, and nothing of consequence is known about metabolic changes. While cataractous human lenses are readily available for study, normal lenses are not, and thus meaningful comparisons are difficult, if not impossible, to make. Moreover, while many animals are subject to senile cataract, these cataractous lenses are not easy to acquire, because it is costly to maintain a colony of animals for years in anticipation that an occasional animal will develop a cataract. Thus, except for a few analyses of normal and cataractous bovine lenses, and even fewer from other animals, there is also a paucity of knowledge concerning the biochemistry of senile cataract in animals.

Other changes which occur in senile cataract include loss of glutathione and ascorbic acid (vitamin C), a rise in cholesterol and calcium, and a general

equilibration of other electrolytes between lens and intraocular fluids, which is a characteristic of dead and dying tissues generally.

Because of the unique immunologic properties of the lens it is possible that cataractous changes associated with age may be an immunologic response to lens antibodies formed within the body of the individual. Proteins in the lens, unlike those found elsewhere in the body, are organ specific rather than species specific, presumably because they are inaccessible to the immune system during prenatal life. Thus, potentially, lens proteins may act as foreign bodies throughout life if they enter the blood and produce antibodies that, through reaction with proteins in the lens, could result in loss of transparency.

There is little evidence, however, that lens antibodies are involved in the pathogenesis of senile cataract, since none have been found in the sera of patients with cataract. Neither is there evidence of lens damage in animals that do have high titers of antibodies, although some offspring of female rabbits immunized with lens protein have a high incidence of cataracts. Actually, lens antibodies are present in about half of a healthy population of patients without lens cataract or any ocular disease.

Despite extensive studies of metabolic and other changes in the lens associated with the aging process, no clues to the genesis of senile cataract have been uncovered.

Surgical Techniques

While research thus far has not provided a medical treatment for cataract, many technical improvements have made cataract surgery safer and more satisfactory. Advancements have been made in suture techniques, improved instrumentation, and in operation under microscopic control. The use of a proteolytic enzyme, alpha chymotrypsin, has made it easier to free the cataract from its attachments (zonules), thus simplifying the operation. Cryogenic or freezing procedures that facilitate removal of cataracts have also been adapted to ocular surgery.

FUTURE APPROACHES

Little is known regarding the transmission of light through the structural proteins of the lens, or how it is affected by alteration in hydration or by the change in the ratio of soluble to insoluble protein which occurs in older lenses. However, optical homogeneity is impaired by any change in the physical state of the proteins of the lens which affects the high degree of spatial order in the lens fibers. Future investigations therefore should be directed toward obtaining a better understanding of the physical and chemical characteristics of lens proteins such as their number, size, structure, immune properties and the chemical relationship of different kinds of protein fractions to each other. Essential also is the determination of their amino acid composition and sequence of these compounds in the protein molecule, as well as the role of nucleic acids in protein synthesis and the mechanism by which normally soluble proteins become insoluble, a process ordinarily accompanied by clouding of the lens.

It is important to learn more about the laws and mechanisms governing the formation and maintenance of the small unit protein aggregates which are now known to comprise the soluble lens proteins. The factors needed to preserve the chemical integrity of lens proteins despite advancing age should be determined and the changes in protein chemistry which occur in various forms of experimental and human cataract require elucidation.

Future research should stress too the broader aspects of lens physiology and biochemistry not directly related to proteins. Preferably, these investigations should be conducted at a subcellular level and be designed to provide further knowledge about energy metabolism, transport mechanisms, osmotic equilibria, and other factors which control cell function. The effects of age, and of various agents known to produce cataracts, on each of these parameters, must also be investigated to uncover possible cause-and-effect relationships in cataract production. Seldom will it be sufficient to study the lens as a whole, since the capsule, epithelium, cortex and nucleus have many dissimilar properties and functions.

Lastly, and most important, is the question of how to obtain better insight into the pathogenesis of senile cataract. One possibility, given sufficient funds, is to conduct parallel investigations on the lenses of dogs, in which senile cataracts are common, and in cats, in which they apparently never occur. Another approach might be to conduct a thorough investigation of the natural history and epidemiology of senile cataract in several geographic areas in this country and abroad. Such a study would have to be carried out by a thoroughly skilled and multidisciplinary team.

The task is an enormous one, but with recent advances in techniques and instrumentation, and increased knowledge in other scientific areas, an effective prophylactic agent or a satisfactory medical treatment for cataract might be found.

Dr. D. V. N. Reddy assisted in collecting data for this report and made many helpful suggestions in its preparation. Dr. Harry Maisel provided material for the section concerned with immunology and Dr. Abraham Spector for much of that pertaining to protein chemistry.

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Chapter II—UVEITIS

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INTRODUCTION

"Endogenous uveitis" is the term used to describe a nonpurulent inflammation of the eye. Uveitis implies that the primary site of the inflammatory response is in the uveal tract. In many instances, however, this is not the case: for the causative organisms or antigenic stimulus may be located in the retina (as in toxoplasmosis, cytomegalic inclusion disease, syphilis, and tuberculosis), the lens (as in phacoanaphylactic endophthalmitis), and the vitreous (as in nematode endophthalmitis, postoperative uveitis, and possibly "pars planitis"). In still other conditions, the primary site of the inflammation may be in the perivascular tissues, as in Behcet's disease; and finally, in some cases such as sarcoidosis, many layers of the eye may be involved simultaneously—i.e., the sclera, uveal tract, retina, vitreous, cornea, and so on.

In most reactions, the source of the inflammation is endogenous and enters the eye by way of the bloodstream (as in toxoplasmosis, syphilis, and cytomegalic disease) or possibly by way of the intraocular nerves (as in herpes zoster). In other types of uveal inflammations, such as acute nongranulomatous iridocyclitis, the cause of the inflammatory response is thought to be an antigenic stimulus that enters the eye either from the intraocular blood vessels or from some exogenous source. In some attacks, however, such as those related to herpes simplex, the organism is known to enter the eye through the cornea. In sympathetic ophthalmia, it would appear that some exogenous factor is needed to initiate the uveal disease, for this condition rarely occurs without a laceration of the globe.

It is obvious from the above discussion that uveitis is not a single entity, but an inflammation of the ocular tissues that can be caused by many agents and factors. The clinical pictures thus produced are not always clear-cut, but overlap one another considerably. Even in as distinct a reaction as in toxoplasmic retinochoroiditis, the lesion may vary from a single focus the size of a disc to involvement of nearly all layers of the eye, or an endophthalmitis. For this reason, some clinicians feel it wiser to classify uveitis merely into anterior and posterior involvement, and acute or chronic inflammation, rather than attempting to establish specific disease pictures (*1*). Others believe, however, that because of the multiple causes of ocular inflammations, statistical correlations with specific agents cannot be obtained until the ocular response is broken down into clinical entities (*2*).

The importance of uveitis as a socioeconomic factor is not known at the present time; for in many instances, it causes a loss of only one eye, or a partial impairment of vision in both eyes, rather than legal blindness. In addition, in the studies that have used legal blindness as an index of blinding eye diseases, such as "The Causes of Blindness in Canada" (*3*) and in the report of the National Society for the Prevention of Blindness (*4*), uveitis as listed refers only to those patients whose disease began with an inflammation of the uveal tract. There are many other instances, however, where the uveal inflammation is the secondary cause of blindness—for example, following cataract extraction, operation for glaucoma, or corneal infection. Nonetheless, uveal inflammation is listed as a primary cause of blindness in 6.5 percent of the cases reported in the Canadian study and in 3 percent of those reported by the National Society for the Prevention of Blindness.

Some difficulties involved in studying ocular inflammation result from the anatomical peculiarities of the eye. A lesion a millimeter or two in size can produce legal blindness if it is located in the macular area. Ordinarily the eye contains few lymphocytes and plasma cells, but after the introduction of a foreign antigen these cells increase in number. When the inflammation subsides, the eye appears clinically entirely normal. Histologically, there is a slight increase in the number of small lymphocytes over those normally found. When the antigen reenters the eye, months or years later, the activation of these cells and the union of antigen and antibody cause sufficient hyperemia and leakage from the blood vessels to result in an intraocular inflammation very similar to that seen in acute nongranulomatous uveitis. A similar response in the lymph nodes would probably go entirely unnoticed (*5*).

Another factor which makes the study of uveal inflammation extremely difficult is the unavailability of ocular tissues for laboratory study during the acute stages of the inflammatory process. Biopsies cannot be taken because they may destroy vision; globes do not become available until the disease has run its course and the eyes have had to be enucleated because they are blind and painful. Thus, the necessary histopathological and microbiological studies during the active course of uveitis are lacking; and only old, burned-out lesions with a nonspecific picture are available for analysis. (Some rare exceptions to this statement will be listed below.)

TYPES OF CLINICAL RESPONSE (EXAMPLES ONLY)

Sympathetic ophthalmia is one exception, for very frequently eyes are removed during the first few days of this type of inflammatory response. Unfortunately, however, cultures, histological studies, and other techniques have failed to reveal a causative organism. It is suspected that this disease is some form of autoimmune response to the uveal tissue. Numerous studies in experimental animals, however, have failed to reproduce this clinical picture. Probably the most impressive evidence for autoimmunity in this condition is the reaction to a heterologous uveal-pigment skin test that quite closely simulates the histological picture of the uveal inflammation.

In addition, there are a number of clinical lesions, such as Behcet's syndrome, Harada's syndrome, and heterochromic iridocyclitis, that are well-established clinical entities; however, in spite of these and the listings above, there are still many causes of uveitis that do not fall into a specific category and for which there is no known causative factor.

The best-documented etiological factor in endogenous uveal inflammation has been the protozoa *Toxoplasma gondii*. The finding of this organism in the retina in histopathological material in a great number of eyes (*6–8*) and the isolation of the protozoa from some of these and other specimens have placed the etiological diagnosis on a firm footing. This is an excellent model for the study of uveitis, for it occurs in patients who are otherwise well, but have a high incidence of serological evidence of systemic disease. The lesions also occur both in children with congenital toxoplasmosis and in adults with systemic toxoplasmosis.

Nematodes, specifically the *Toxocara canis* and *T. mystax*, have been found to produce three types of ocular inflammation. First, an endophthalmitis; second, a nodular macular lesion; and third, an isolated focal lesion in the periphery of the globe. The inflammatory response in this type of ocular infection is located on the track through which the nematode has migrated, or in the area where the organism has lodged. The site of greatest inflammation is frequently in the vitreous, and in these cases it is easy to differentiate these lesions both histologically and clinically from other types of uveal inflammation.

Patients with leprosy, leptospirosis, and onchocerciasis are all known to have ocular inflammation, and the specific organisms have been isolated from the uveal tissue (*9*). However, these diseases are extremely rare in this country.

A few viral and fungal agents have been isolated from the eyes of patients dying from systemic infections with these organisms, but these specimens are so rare as to be considered clinical oddities.

Patients dying of sarcoidosis have also been found to have histologically typical lesions in their eyes, but the etiology of this disease is unknown.

Acute, nongranulomatous iridocyclitis is thought to occur more frequently in patients with Strümpell-Marie ankylosing spondylitis and ulcerative colitis than one would normally expect. A chronic, nongranulomatous iridocyclitis with very little external manifestation of ocular inflammation occurs in children with Still's disease.

The most convincing type of autosensitivity occurs in patients who have become sensitized to their own lenses. There have been suggestions in the literature that this clinical entity could be reproduced in experimental animals; however, evidence for this is not totally convincing (*10*). Again, this lesion usually results from a penetrating wound to the eye, such as trauma, or under surgical procedure where the lens capsule has been ruptured. This suggests that some form of adjuvant is needed to initiate the process.

METHODS OF STUDY

The methods that have been used in the past to study this problem have been attempts to produce a similar lesion in experimental animals and to perform clinical and laboratory studies on man. Uhlenhuth in 1903 first observed that autohypersensitivity could be produced by injecting animals with material taken from their own lenses (*11*). Since that time, numerous attempts have been made to produce a chronic ocular inflammation in experimental animals by injecting these animals with autologous, homologous, or heterologous ocular material. These substances hase been given with and without Freund's adjuvant (*12*).

Various antigens have been injected into the eye, and it has been shown that, once sensitized, the eye reacts with an inflammatory response when the antigen is reintroduced either into the globe or, if in sufficient dosage, systemically. The study of just what happens in the eye during this process is the subject of considerable interest at present. It should be mentioned that ocular inflammations produced

in this manner very closely simulate nongranulomatous anterior uveitis in man.

Another method of inducing ocular inflammation experimentally has been to inoculate various species of animals with a number of viral, bacteriological, and fungal agents. In some instances, either ocular or systemic inoculations into the immune or nonimmune animal have produced a nonpyogenic inflammation somewhat similar to that seen in man. However, in practically all instances, the essential feature of a chronic, recurring disease has not been attained in experimental animals. A spontaneous, recurring uveal inflammation that occurs in chickens is quite similar to the picture seen in man; but this disease, or experimental model, has attracted little attention from the ophthalmic point of view (*13*). Much is known about the virology of avian lymphomatosis, the systemic manifestation of this disease.

From a clinical point of view, since pathological material is not readily available from uveal inflammations in man, studies have been limited to skin tests and serological evidence of systemic diseases that have been thought to be possible causes of ocular inflammation. In spite of some interesting observations that have been made from this type of investigation, none of the studies of this type have used adequate controls (as demanded by modern epidemiology).

Aronson (*14*), and Wood and Perkins (*15*), have found that a higher percentage of patients with uveitis have humoral antibodies to uveal tissue than do normal individuals. However, persons with ocular disease other than uveitis also have a higher percentage of circulating antibodies to uveal tissue than do normal individuals. Thus, it appears that these antibodies may merely represent damage to the eye, rather than indicating that autohypersensitivity plays a part in uveal inflammation.

Numerous examinations have been made of the aqueous in search of some specific cytological change or organism in uveal inflammation. In a few cases where the reaction has been caused by the virus of herpes simplex, a fungal infection, or a bacterial infection, these studies have been quite unrewardinfection, these studies have been quite valuable. Unfortunately, however, in most instances, they have been quite unrewarding. Witmer (*16*) has recently made the interesting observation that, in some specific types of inflammation, antibody titers due to supposed causative organisms are higher in the anterior chamber than in the circulating blood. This technique may be a promising one for future investigations.

EPIDEMIOLOGY

The epidemiology of uveitis has not been thoroughly studied in this country. On a worldwide basis, however, it is known that onchocerciasis, leptospirosis, leprosy, and Chagas' disease occur only in certain parts of the world (*9*). It is also known that sympathetic ophthalmia is much less common in the Negro than it is in the Caucasian, both in America and in Africa. There is a great need for epidemiological studies of uveal inflammation in this country, and even for studies on the natural history of its specific types (*17, 18*).

One such study is now in progress in Cincinnati, Ohio (*19*). This is being done on small, punched-out areas of chorioretinal atrophy in the periphery of the fundus and a hemorrhagic detachment of the retina in the macular area. The lesion has been associated in a high percentage of cases with a positive histoplasmin skin test. A few eyes with active lesions of this type have become available for histological examination; but to date, the *Histoplasma capsulatum* has not been found in these specimens. Dr. Asbury is therefore performing fundus examinations on a large number of persons in the Cincinnati area who have no ocular symptoms, but who have positive or negative histoplasmin skin tests. He hopes to determine whether there is a statistically significant difference between the number of patients who have peripheral punched-out lesions in the fundus and a positive histoplasmin skin test, and the number of those with a negative skin test and normal fundi.

Only at the University of California is there a significant concentration of scientific personnel studying various factors of uveal inflammation.

Work in progress on uveitis in other parts of the world is more difficult to pinpoint and assess. Dr. Rudolf Witmer of Zurich, Switzerland, is probably the most active investigator outside of the United States. Dr. E. S. Perkins (*20*) of the University of London is also active in this field, as is Dr. Hans Remky of Munich, Germany (*21*).

TREATMENT

As would be expected when so little is known about the pathogenesis and etiology of a condition, treatment of uveitis is usually nonspecific. Corticosteroid therapy appears to suppress the uveal inflammation, at least in part, in most cases. However, since it is not curative, the eye frequently proceeds on a downhill course unless the condition is self-limited. Even in the case of toxoplasmosis, where a specific clinical picture has been correlated with the isolation of the causative organism, specific treatment is of little value. At least two factors may play a part in this. One, the ocular lesion may be produced as a result of the antigen-antibody reaction; and, two, the organisms may survive in the eye because they are primarily in the encysted form and

are therefore not destroyed by Daraprim® and sulfadiazine therapy. Also, since the eye is encased by a watertight covering, the necrotic products following destruction of tissue may produce a uveal inflammation long after the causative organism has disappeared. This is frequently seen in patients with purulent panophthalmitis, where the organism has been destroyed by antibiotics, but the inflammation persists because of the necrotic tissue in the eye.

One should not assume, however, that all uveal disease caused by a specific organism will not respond to therapy; for there are instances, such as in secondary syphilis and in disseminated miliary tuberculosis, where the ocular lesion responds quite rapidly after the use of appropriate drugs. Other agents which may prove to be of value in the future are Butazolidin,® indomethacin, and some of the alkylating agents.

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Chapter 12—DISORDERS OF THE RETINA AND CHOROID

Not Including Uveitis, Neoplasms, Diabetic Retinopathy, Physiology of Vision, Defects of Color Vision or Dark Adaptation

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INTRODUCTION

The retina is the nervous tissue which lines the eye and converts light to nervous stimuli which are transmitted to the brain. It is an immensely complicated structure and not only reflects disorders occurring immediately within it but is an integral part of the central nervous system. Its blood vessels can be viewed by means of special instruments and a variety of systemic disorders are diagnosed by means of visible changes in these vessels. The choroid is a specialized vascular tissue immediately adjacent to the retina. Its most important function is provision of nutrition for that portion of the retina which touches it. Choroidal disease can give rise to disturbances in the overlying retina and in many cases it is not known whether a disease involves the choroid or the retina.

Diseases affecting the function of the retina are important causes of blindness. It is the purpose of this report to focus on this structure and on specific diseases affecting it. Certain diseases, such as abnormalities of blood vessels and color vision, are considered in other reports.

A brief description of the manifestations of retinal diseases will be given here. Research attempting to give us a better understanding of both the normal and diseased retina will be discussed. Finally, important problems to be solved and recommendations will be considered.

CLASSIFICATION OF RETINAL DISEASE

Retinal abnormalities reflect a primary disease of some layer or layers of this structure, a blood vessel disease, or an abnormality of one of the adjacent structures, the choroid or vitreous. Often we are not certain where the initial changes occur and therefore can only speak of changes which involve many layers. In the classification given here the disease is listed according to proven or suspected sites of initial disease where this is possible.

A. Ganglion cell degenerations
   1. Lipoid infiltration diseases
   2. Cerebro-macular degenerations
B. Degenerations of the inner nuclear layers
   1. Cystoid degeneration
   2. Circinate retinopathy
C. Receptor cell abnormalities
   1. Cones
      a. Total color blindness
      b. Cone degenerations
   2. Rods
      a. Congenital night blindness
   3. Rods and cones
      a. Congenital tapetoretinal degenerations (Leber's amaurosis congenita)
      b. Retinitis p gmentosa
      c. Some macular degenerations
D. Pigment cell abnormalities
   1. Deficiency of pigment
      a. Albinism, various forms
   2. Storage of toxic substances
      a. Chloroquine
      b. Mellaril
   3. Abnormal secretions
      a. Vitelline macular degeneration
E. Bruch's membrane abnormalities
   1. Fundus albipunctatus
   2. Fundus flavimaculatus
   3. Colloid bodies
   4. Angioid streaks
F. Degenerations of both choroid and retina
   1. Malignant myopia
   2. Choroidal sclerosis
      a. Central (central areolar sclerosis of Sorsby)
      b. Peripheral
   3. Choroideremia
   4. Gyrate atrophy

G. Vascular
   1. Venous
   2. Arteriolar
H. Retinal separations
   1. Retinal detachment
   2. Retinal schisis
I. Coat's Disease

CLINICAL PICTURE OF THE DISEASE

The common denominator of retinal disorders is loss of vision. There may be a highly selective loss of certain visual functions with retention of other functions. Thus, macular degenerations cause a diminution of central visual acuity with peripheral vision preserved. Retinal detachments cause a loss of peripheral vision with the central visual acuity preserved. In some instances there is selective loss of color vision with other visual functions normal. The diagnosis is based essentially upon a comprehensive eye examination with determination of central visual acuity, quantitative evaluation of the visual fields, measurement of color vision, and careful study and skilled interpretation of the appearance of the back of the eye by means of special instruments. The most common of these instruments, the ophthalmoscope, is often combined with additional specialized equipment to provide a stereoscopic view of the retina or a highly magnified view. It may often be difficult to determine the nature or the cause of a retinal disorder but usually it is evident when some abnormality of the retina is at fault in causing decrease in vision.

DIAGNOSIS

The diagnosis of retinal disease is aided by direct examination and by tests which measure the function of this nervous tissue.

Techniques of examination have been improved both in the area of ophthalmoscopy and of supplemental aids used with ophthalmoscopy. The indirect ophthalmoscope has helped greatly in the evaluation of retinal detachments (*1*). Fluorescein angiography has been extensively pursued in the last few years. Norton (*2*), Heyman (*3*), and Maumenee (*4*) and many others are using this technique to delineate the function of the retinal vasculature. This method has been of aid in delineating the nature of retinal and choroidal lesions.

Two groups are investigating television ophthalmoscopy as a means of studying the retina in greater detail (*5, 6*).

More sophisticated means of measuring retinal function have become available at many institutions in the last few years. Included in this area are psychophysical tests such as color vision and dark adaptation studies, and electrophysiological tests such as the electroretinogram, the electro-oculogram, and evoked occipital potentials. Data accumulated in the various retinal disorders with these tests allow more exact characterization of the diseases. Diagnoses are thus made with more certainty and, more importantly, early forms of diseases can sometimes be detected with these tests. This is important since these are the kinds of patients which in the future may be susceptible to treatment. Some of these tests have aided in the detecting of carriers. Of course, it is necessary to study the range of normal findings before being sure of early or minimal abnormalities.

Psychophysical studies in both normal and diseased patients are being done by Mathew Alpern (*7, 8*) of the University of Michigan, Jay Enoch (*9*) at Washington University, Alex E. Krill (*10, 11*) at the University of Chicago, H. Richard Blackwell (*12*) at Ohio State University, Gerald Westheimer (*13*) at the University of California School of Optometry, Harris Ripps (*14*) at New York University and Ernest Wolf (*15*) at the Retina Foundation. Electrophysiological studies in normal subjects and diseased patients are being conducted by Hermann Burian (*16*) at the State University of Iowa, Jerry Jacobson (*17*) at Cornell University, George Goodman (*18*) at New York University, Alex E. Krill (*10*) at the University of Chicago, Lorin Riggs (*19*) at Brown University, Jerald Pearlman (*20*) at the State University of Iowa, and Arthur Jampolski (*21*) at the San Francisco Institute of Medical Sciences. George Goodman has been particularly interested in evaluating the various types of myopia. Jerald Pearlman has been studying the electroretinogram in thyroid disease. Alex E. Krill has been interested particularly in electrophysiological and psychophysical studies in carriers of various diseases. Both Mathew Alpern and H. Richard Blackwell have been particularly interested in patients with color vision defects.

Richard Copenhaver (*22*) at the University of Florida, Albert M. Potts (*23*) of the University of Chicago and Jerry Jacobson (*24*) at Cornell University have been studying evoked occipital potentials using focal retinal stimuli. This technique may be a sensitive objective means of studying macular function. Carr, Gouras, and Gunkel (*25*) are using perimetric colored and white absolute thresholds as a method for the detection of early chloroquine retinopathy.

These various studies have been important in gaining a better understanding of the retinal and choroidal abnormalities. They help in delineating the extent of the disease and the prognosis of a particular disease. The tests have also aided in classifying the various abnormalities. Of particular interest have been findings in various macular diseases.

Where ophthalmoscopic evaluation has shown isolated macular lesions, tests such as the ERG and EOG often have indicated an abnormality of much greater extent.

ETIOLOGY

Basically the etiology of retinal disorders involves the following systems:

1. Disorders of the nervous tissue of the retina itself.
2. Disorders of the pigment lining of the retina.
3. Disorders of the blood supply via the central retinal artery.
4. Disorders of the blood supply via the choriocapillaris. Included in the etiology is damage from radiation, injury, drugs, toxic effects, hereditary disorders, and the like.

A. Franceschetti (*26*) and his group in Switzerland are studying the genetics of tapetoretinal degenerations. Aleta Barker (*27*) at Louisiana State University is conducting a study of genetic factors for blindness. It is important to gain an understanding of the exact inheritance of these various diseases. Prediction of how many members in a family may be affected and of the effect on future offspring are important practical considerations.

Albert M. Potts (*28, 29*) at the University of Chicago is studying the biochemistry, electrophysiology, and histology of the retina with methanol poisoning and glutamate toxicity. He is also studying the metabolism of phenothiazines and antimalarial drugs in the hope of eventually obtaining rational therapy against toxicity with these drugs. Howard M. Bernstein (*30*) at the Eye Research Foundation of Bethesda is studying the pharmacology and retinal toxicity of chloroquine. J. Fraser Muirhead (*31*) at the University of California is studying the mechanisms of phenothiazine toxicity.

PATHOPHYSIOLOGY

One of the great limitations in the study of retinal disorders is the paucity of human eyes which have been available before death for histologic examination. Only primates have eyes comparable to man's and studies from other species are extrapolated to man with difficulty. On the other hand, numerous institutions have first-class eye pathology laboratories that are doing outstanding work. By means of injection techniques and special stains, information concerning diseases of the retina is accumulating.

Electron microscopic studies of the retinal and choroidal tissues are being conducted by George K. Smelser (*32*) at Columbia University, Michael J. Hogan (*33*) at the University of California, Maurice H. Bernstein (*34*) at Wayne State University, David G. Cogan (*35*) at Harvard University and John E. Dowling (*36*) at Johns Hopkins. The latter author is attempting to relate electron microscopic findings to retinal function. It would appear that there are certainly adequate studies of normal tissues. Raymond A. Allen (*37*) of the University of California is using the electron microscope to study retinal bipolar cells. Eichi Yamada (*38*) of Kyushu University in Japan and Jerome Wolken (*39*) of the Carnegie Institute of Technology are studying photoreceptors with the electron microscope.

George K. Smelser (*32*) at Columbia and E. Carl Sensenig (*40*) at the University of Alabama are studying the embryology of the eye. Austin H. Riesen (*41*) of the University of California is studying developmental defects, particularly in monkeys, caused by raising the animals in special environments; he is particularly interested in the effects produced by raising the animals in complete darkness for varying periods of time.

Oliver H. Lowry (*42*) of Washington University and David Cogan (*35*) of Harvard University are studying the histochemistry of the retina. The biochemistry of retinal pigments is being studied by Ruth Hubbard (*43*) of Harvard University, Alan Kropf (*44*) of Amherst College and Edwin W. Abrahamson (*45*) of Case Institute of Technology. Harris Ripps (*46*) of New York University and R. A. Weale (*46*) at the University of London are using fundus reflectometry to study cone pigments in the normal human fovea. Vera Glocklin (*47*) of the University of Chicago is studying the metabolism of the pigment epithelium cells. Sidney Futterman (*48*) of the Massachusetts Eye and Ear Infirmary is studying various aspects of retinal metabolism. David Cogan (*35*) at Harvard University is studying the electron microscopy of retinal dehydrogenase. David G. McConnell (*49*) of Ohio State University is engaged in chemical studies of the stimulated retina. Marvin L. Sears (*50*) of Yale University is studying retinal metabolism of the retina. Frank W. Newell (*44*) of the University of Chicago is studying the carbohydrate metabolism of the retina. Jay Enoch (*51*) of Washington University is using histochemical stains to differentiate between the light and dark adapted retina. Newer biochemical techniques are being utilized to fully understand the working of the structure in its normal state.

At the National Institutes of Health the group under Ludwig von Sallman (*52*) is studying the role of the choroid in nutrition of the retina in the cat. Ischemia of the choroid is produced by injecting a thrombosing agent into a vortex vein. Ephraim Freedman (*53*) of the Massachusetts Eye and Ear Infirmary is studying retinal microcirculation. Regina Frayser (*54*) of Indiana University is studying the retinal circulation in general. J. O'Rourke (*55*)

of Georgetown University is studying uveal blood flow and metabolism in vivo. Jerome Bettman (*56*) of Presbyterian Hospital, San Francisco, is studying the effects of agents on the choroidal blood flow. A clear understanding of the dynamics of the choroidal and retinal vascular systems may be important for many reasons. For instance, senile macular degenerations, the cause of 29 percent of all blindness in the United States and the third most common cause of blindness in Canada, are frequently secondary to vascular changes in the choroidal circulation.

George Wise (*57*) at New York University is conducting ophthalmoscopic examinations of criticallist patients and obtaining eyes for pathologic studies. The exact nature of the disease can be determined only by pathological studies. Studies correlating clinical and pathologic studies are of the utmost value.

Edward Okun (*58*) at Washington University, St. Louis, is studying experimental retinal pathology. Retinal holes and other changes which may relate to detachments are evaluated in this study. Arthur F. Howe (*59*) of the Retina Foundation is conducting chemical and immunochemical studies of the vitreous body. Angelos Dellaporta (*60*) is studying idiopathic retinal detachment. Bradley R. Straatsma (*61*) at the University of California is evaluating the relationship of mucopolysaccharides to retinal detachment. Harvey A. Lincoff (*62*) at Cornell University is evaluating the cryosurgical treatment of ocular disease, including retinal detachments.

James McGinness (*63*) at Washington State University is studying eye and brain damage under continuous light. William V. Lovell is studying a modified Lovell eye magnet for nonmagnetic materials. Werner K. Noell (*44*) at the State University of New York at Buffalo is studying the vulnerability of the retina to light and other agents.

EPIDEMIOLOGY

The incidence of retinal disease often may be difficult to determine. Many of the diseases affect the very young or the very old and they are not identified in routine surveys. Some diseases affecting the very young result in premature death. The aged may not complain if they are not accustomed to use of the eyes for fine work and are not unusually dependent upon reading. In most registries, diseases of the retina account for approximately 40 percent of all registered blind. Some 29 percent of these are due to senile macular degeneration, 9 percent to choroidal atrophy, 3 percent to vascular disease, 2 percent to retinitis pigmentosa, and 1 percent due to retrolental fibroplasia. The statistics vary in different groups and the judgment of etiology depends on the care with which the examination is carried out. In many surveys the retinal vascular changes arising because of diabetes mellitus are included as a type of retinal degeneration, and the exact statistics are difficult to determine. This may be the reason that approximately twice as many cases of blindness due to retinal disorders, not including diabetic retinopathy, have been reported in England and Wales, than in Canada.

TREATMENT

The outstanding success in the treatment of retinal degeneration has been the cure of retinal detachment by means of surgery. Until 1928 when Gonin indicated the role of localized areas of degeneration (retinal breaks) in the development of detached retina, there was no effective treatment. In recent years more and more detached retinae are being treated effectively by means of specialized surgical techniques. In addition, the construction of sources of intense light which can be controlled and focused has resulted in the cure of certain kinds of retinal detachments without surgery. The recent use of freezing temperatures in retinal detachment surgery may also prove to be of greater value than standard diathermy techniques used.

Albert M. Potts (*28*) at the University of Chicago has been trying drugs which may compete with phenothiazines in patients with chloroquine toxicity. Louise Sloan (*65*) at Johns Hopkins is studying various kinds of optical aids to be used for patients with retinal diseases. Of course, the ultimate aim is to offer some type of treatment for the various conditions, either symptomatic or preventive in early cases.

ELIMINATION

The outstanding event in ophthalmology since 1950 has been the elimination of retrolental fibroplasia by preventing high doses of oxygen to premature infants. This disease which at one time was causing 7,000 infants annually to become totally blind has been virtually eliminated. Unfortunately it has not been possible to eliminate other forms of retinal disease (*65*, *66*, *67*).

RECOMMENDATIONS

There is a need to investigate the pathology, biochemistry, and neurochemistry of tissues from affected individuals. For many of the diseases referred to above, there has never been even one study of the underlying tissue changes.

There is great need for correlating histological changes in the macular region and other areas of the

retina with clinical appearance and retinal function evaluation. This is being done at only a few institutions.

There is a great need to study the vasculature of the retina and choroid, particularly in the disease states, and to correlate changes with ophthalmoscopic changes and retinal function changes.

Sophisticated means of retinal function evaluation, both psychophysical and electrophysiological, are needed in many more centers. Such testing is only available at a few universities at the present time. Better classification, early diagnosis, detection of carriers, and a better understanding of the physiological abnormalities in retinal diseases are some of the gains from such testing.

There is a great need to study early cases of the various diseases. It is important to study these patients very thoroughly from the standpoint of possible blood abnormalities, biochemical abnormalities, and functional evaluation. From such studies possible modes of treatment may be inferred.

It is important to study carriers of diseases with sex-linked or autosomal recessive inheritance. A better understanding of the physiology of disease and of the early forms of the disease will be gained in this manner. It is noteworthy that early forms of a particular disease may resemble a carrier state, particularly in sex-linked disease.

Epidemiological studies are necessary to define the genetics, extent, and complete clinical picture of many retinal diseases. Field studies in endemic areas for certain retinal diseases should be done. Albinism has been reported in certain Indian groups (Hopi and Pueblo) and a large sample would be available for different types of studies. Total color blindness and retinitis pigmentosa, which are most frequently autosomal recessive diseases, are found in rather high frequency in some of the mountain areas of Kentucky and West Virginia. If facilities were available in these areas, it might even be possible to obtain tissue specimens from diseased individuals.

In some areas more exact diagnoses are needed. This is particularly true in schools and institutions for the blind or partially sighted. Many children have incomplete or no diagnoses. Retinal function evaluation would be of particular value in these children who often have only minimal or inconclusive eye findings.

The rehabilitation available to patients with retinal degeneration is disappointing. In some instances specialized lenses may be used and a number of devices have been developed for reading but they require intense concentration and oftentimes allow only a limited field to be seen. Much more work on optical aids is needed.

It is important to finance symposia concerning retinal detachments so that surgeons can keep abreast of the latest developments. More studies on the nature of subretinal fluid and the vitreous body are needed. The ideal plastic material is still not available for retinal surgery. The engineering of a cheaper photocoagulator should be considered. The high cost of this instrument prevents the widespread use of photocoagulation, which is of proven merit in certain conditions. More suitable vitreous replacement substances are needed.

Development of a suitable instrument for nonmagnetic extraction has been a long-term wish of the ophthalmologist. Up to this time no instrument has proven entirely satisfactory.

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Chapter 13—SYSTEMIC DISEASES AND THE EYE

Systemic Diseases That Produce Ocular Dysfunction Other Than Diabetes Mellitus

I. General Aspects
II. Research Approaches

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I. GENERAL ASPECTS

Infective Disease

There are many viruses, bacteria, fungi, and protozoa that invade the eye alone, but many more that induce ocular infection in association with attack on other body tissues.

The problems in infection involve identification of etiologic organism, measures to stimulate and increase natural resistance, supportive therapy, and anti-inflammatory therapy. The latter will be specific where such agents are available. In spite of the many wonderful antibiotic and chemotherapeutic compounds, eyes are lost to infection. There are many reasons for this.

Postoperative infections must be treated with antibiotics selected on an empirical basis. Although treatment based on the results of a culture and the specific antibiotic sensitivity of the offending organism would be scientifically ideal, the rapidity with which an eye is destroyed precludes the initial therapy from being so accurately selected. Culture of the external eye, even in the most overwhelming infection, will not reveal the offending organism in the majority of cases. The surgeon often has qualms about reopening the operative wound for an ocular culture for fear of additional complications and because even these cultures are frequently negative. Preventive measures in such infections should continue to be investigated. Newer methods are needed for earlier and more specific diagnoses.

The penetration of therapeutic agents from the bloodstream into ocular structures and tissues is usually less rapid and less intense than into other body tissues. The eye and the central nervous system have similar penetration characteristics. This necessitates determination of the blood/aqueous and blood/ocular-tissue ratio in the normal and in the inflamed eye for each new agent.

Each of the agents has a toxicity for body tissues. Ocular-tissue tolerance and toxicity development may differ from those of other body structures and must be evaluated.

Dosage schedules for the various agents have to be developed on the basis of penetration and toxic studies in the experimental animal, as well as through trials versus experimental infections. The final dosage can only be established after human tests of a similar nature and after a definite period of time.

The table in appendix A gives an overall picture of infections involving the eye.

Noninfective Systemic Disease

There are a variety of noninfective systemic diseases which can produce ocular changes that are vision-threatening or destructive to vision. The etiologies of many of these diseases are not known. The therapy is often unspecific, symptomatic, or indirect (see app. B).

In the majority of these diseases, more information is required on causation, incidence, frequency, diagnosis, and therapy.

Inherited enzymatic defects may account for these disorders. At present, early detection usually fails to prevent the ocular complications, but it does help. There are other disorders which probably fit in this group that involve the eye. Research in the field merits continued support.

Drugs used for therapy have produced complications. Antimalarial agents tend to accumulate in ocular tissues and produce disorders. The lesions induced resemble other forms of ocular disease, such as retinal degeneration and macular degeneration. Studies directed to the mechanism of this drug effect may provide an answer not only to drug intoxication, but also, possibly, to the nonspecific degenerative diseases that are not drug related. It might even be possible that these degenerative diseases are examples of hereditary inadequacies of the enzyme

systems necessary for detoxification, drug breakdown, and metabolite and tissue catabolism.

As new medical discoveries permit increased longevity, the degenerative diseases of the eye become more prevalent. Increasing numbers of our older population are becoming visually handicapped from degenerative ocular diseases. Their productivity is curtailed, and some of their main recreational activities during retirement are no longer possible. Degenerative macular changes reduce central vision. Peripheral retinal degeneration associated with changes in the vitreous make the older individual more prone to retinal detachment, especially after cataract extraction. Chronic diseases such as glaucoma, diabetic retinopathy, and uveitis frequently tend to progress with age. The need for work in this area of degenerative diseases is overwhelming.

1. *Pharmacologic Agents.*—All of these diseases involve the use of drugs either in diagnosis or therapy. Considerable research support is needed to pursue the problems raised by the use of drugs. At the present time, we are in an era in which a particular disease is studied biochemically, genetically, and at the enzymatic and electromicroscopic levels, so that the fundamental defect can be spotted and an appropriate agent synthesized to counteract the offending factor. Synthetic drugs are evolving that include, among others, hormones, antibiotics, antiviral, antifungal, anticancer, antihypertensive, and anti-inflammatory agents. These are deliberately designed to inhibit or stimulate a particular step in the metabolism of the tissue cell or invading organism.

In the plethora of new agents, attempts have to be made to evaluate each one on a therapeutic-armamentarium scale. Is the new agent more effective than previously employed therapy? If not more effective, is it less dangerous? Is it less expensive?

Ophthalmology has shared in these recent changes. The eye has always afforded a wonderful laboratory in which to determine and evaluate the action of drugs. Local anesthetics were first employed in the eye for surgery. Koller, an ophthalmologist whose last post was at the Mount Sinai Hospital in New York City, introduced cocaine for this purpose in 1884. The significance of this event was immediately recognized as revolutionary in ophthalmology, and a little later, the drug was introduced into general surgery.

Drugs that work on the autonomic nervous system, such as atropine, eserine, and adrenalin, were understood pharmacologically after studies involving the ocular structures. In this manner, a number of agents have been shown to possess additional useful properties. Cortisone was found to work locally when instilled directly into an eye. One of the advantages of ocular therapeutics is that many eye diseases can be treated simply by instilling the medicament into the eye, avoiding the oral, intramuscular, or intravenous routes of administration. More recently, the systemically toxic drug IDU was found to be tolerated in the eye when applied locally. This has merit for the management of some forms of herpes simplex keratitis, a potentially blinding disease.

The eye has proven to be a valuable structure in detecting undesirable side actions of many drugs. Considerable concern over the untoward effects of drugs used in therapy has evoked large and small commentaries, analyses, symposia, panel discussions, and indictments of the undesirable results of the use of drugs.

The nature of these effects varies. They are often called the side effects of drugs, the toxic effects, and the adverse effects. There are other terms such as allergic reaction, intolerance, and idiosyncrasy, or drug-induced disease, disease of medical progress, or iatrogenic disorder.

It is important to understand these terms. *A side effect* is a pharmacologic effect other than one sought for in the particular use of the drug. It might be adverse, or nontherapeutic, or even unpleasant, but not fatal. An *adverse effect* could include a side effect but also includes the nonpharmacologic consequences of drug use—the cosmetic effect of the enlarged pupil after the use of atropine, the population explosion in India resulting from effective antimicrobial therapy, or the geriatic problem which we now have as a result of advances in drug therapy. A *toxic effect* is the consequence of the agent's pharmacologic actions. It is one that is undesirable and a threat to normal physiologic function, if not a threat to life. It may be a consequence of a pharmacologic action that also provides the drug's therapeutic usefulness, or it may be associated with other facets of the pharmacologic properties of the drug. *Drug-induced disease* implies a response to the drug in which a disease results from its use.

Ocular structures can reflect all of these side effects. Within recent years, a variety of ocular changes have followed systemically administered agents. *Tranquilizers* such as phenothiazine derivatives have produced corneal opacties, cataracts, and retinal degeneration. Steroids have induced glaucoma and cataracts, predisposed the eye to infection, and caused edema of the optic nerve heads, simulating a brain tumor. *Antimalarials* and *anticollagen* disease therapy have also produced retinal degeneration as well as corneal changes. *Sulfonamides* and *antibiotics* have produced inflammatory and atrophic disturbances in the optic nerve. *Vitamins* A and D, in excess, can produce corneal opacities.

Agents instilled into the eye can produce undesired changes in the eye and elsewhere in the body. Steroids locally instilled can make glaucoma evident, possibly produce cataracts, and enhance viral, fungal,

and bacterial infections of the cornea. Atropine and other cycloplegics may bring on an acute attack of glaucoma. Anticholinesterase agents repeatedly instilled into the eye may induce systemic signs similar to overstimulation of the parasympathetic system. These are a few examples; many others are known. The hazards are evident. Disease states can occur because of the use of new drugs—so-called medical progress..

These effects must in part be considered as adverse, not just toxic. As a result of these reactions, however, it has been possible to determine hereditary patterns in reactions to drugs. Steroids raise intraocular pressure only in certain individuals. Not everyone shows these side effects with each drug. Is that because they have different enzyme systems for breaking down the drug? Or does the enzyme look the same biochemically, but have a few differentiating characteristics?

It is important to avoid side effects, toxic effects, adverse effects, and drug-induced diseases by proper evaluation prior to releasing the agents for general use. This is not always possible. It is most important to find out not only why some people react adversely, but what protects the majority against such action. This has led to a new branch of pharmacology called pharmacogenetics, which has been defined as a study of genetically determined variations in animal species that are revealed by the effects of drugs. This has given us insight into the nature of disease processes. Indirectly, side effects of drugs have aided medical progress. Side effects, adverse effects, drug-induced diseases, idiocyncrasies, intolerance, overdosage, and toxicity are overlapping situations that must be determined for each agent. This requires animal and also human investigation. The questions of drug destruction, the enzymatic processes involved, and the hereditary background for the development of undesired effects, as well as research into basic pharmacologic actions, require maximal support.

Although many of these subjects are studied in other areas of medicine, the eye has proven to be a target organ so frequently that it must be considered a laboratory of its own, requiring all the necessary support.

II. RESEARCH APPROACHES

Many systemic diseases have ocular manifestations, as already enumerated. The eye is particularly vulnerable to insult because of the variegated metabolic patterns, routes of nutritional supply, and tissue structures of its component parts. Widely differing derangements may lead to the same clinical picture. A meaningful research approach must take these factors into consideration.

A classification of the natural history of disease (*1*) will be utilized here. To illustrate areas of research needing further development, pathologic processes may be divided into four stages. Stage I represents the genetic and environmental factors that make an individual susceptible to the development of a disease. In Stage II, the disease is established but latent; the affected individual is asymptomatic. Stage III deals with the overt illness and represents the phase with which clinical medicine is most occupied. Stage IV is the postcure or "burnt-out" phase of the pathologic process. A particular phase may at times be ill-defined. Isolated advances within each category will be cited in this study to clarify approaches to disease that are currently being utilized and those for which future applications are needed.

Stage I. The Predisease State

This subdivision rightfully falls into the provinces of genetic counseling, eugenics, epidemiology, and preventive medicine. The susceptibility of the individual to a given disease depends on his genetic makeup and his environment. The relative importance of these two factors varies according to the particular illness.

1. *Genetics.*—Little can be done at the present time to improve the genetic structure of the individual, but his progeny can be protected by intelligent counseling. With the newer therapies, the survival rate in genetic disease is increased and allows perpetration of the genetic material. Presently a significant percentage of patients with retinoblastoma, who previously never would have reached reproductive age, have a normal lifespan. Not only are there more individuals with visual defects from the disease and its treatment, but the gene prevalance is increasing. The risk to society of perpetrating abnormal genetic material has been well outlined (*2*). The ophthalmologist's role is to recognize carriers of abnormal genes. The responsibility of the investigator is to elucidate the hereditary components of the disease, as well as to seek out the more subtle signs, symptoms, and laboratory procedures by which the process may be recognized.

In dominant autosomal traits and in the male with a sex-linked recessive disease, the task of recognition may be relatively simple because of obvious clinical manifestations. However, factors such as the degree of penetrance, the new mutant, and the effect of the surrounding genetic milieu on the abnormal gene may make the dominant character of the disease difficult to detect. Only by complete family studies may the true mode of transmission be determined. Laboratory examinations may be informative; e.g., the still-controversial finding of increased urinary excretion of hydroxyproline in Marfan's syndrome

(*3*). Further elucidation of abnormal biochemical mechanisms would aid in the identification of these individuals.

In the heterozygous state of autosomal recessive disease and in the female carrier of sex-linked recessive disease, a family history may be the only clue to the carrier state. Occasionally, subtle signs may become manifest (*4*). In angiokeratoma corporis diffusum (Fabry's disease), a sex-linked glycolipoidosis, the sole physical finding in the female can be an epithelial corneal dystrophy observable only on slit-lamp microscopy (*5, 6*). Today, with the use of elaborate laboratory tests, many of which are developed only to the research stage, very specific abnormalties may be discovered in the heterozygote (*7*). The carrier state may be recognized in Tay-Sachs disease by a decreased serum fructose-1 phosphate aldolase level (*8*), in galactosemia by a decreased red blood cell galactose-1 phosphate uridyl transferase activity (*9*), and in homocystinuria by the decreased activity of hepatic cystathionine synthetase (*10*). Even if these tests were more available, there remains the fundamental problem of selecting an individual without a family history or physical findings for a specific laboratory determination. Once one of the progeny of a family develops a hereditary disease, the probability of its future occurrence can be ascertained.

The genetic influence on the development of many diseases remains obscure. Progress is being made by large family studies. Some of the difficulties encountered in this type of investigation have been published in relation to coronary heart disease (*11*) and certain mesenchymal diseases (*12, 13*). Genetic markers may be used to detect subtle genetic influences on disease. Sarcoidosis has been found in many members of certain families (*14*) but often appears de novo, without any evidence of a hereditary tendency. Recently, it has been shown to occur with a greater frequency in persons having blood group A than in those having blood group O (*15, 16*). The incidence of hemoglobinopathies has been found to be significantly higher in sarcoidosis than it is in the general population (*17, 18*). Whether patients with sarcoidosis actually carry a "gene" for sarcoidosis or whether the genetic substrate changes the internal milieu sufficiently to make certain individuals more susceptible to the disease is unknown.

Animal inbreeding experiments help to ascertain the genetic influence on certain diseases. Dahl, et al. (*19*) were able to breed populations of rats highly sensitive and highly resistant to experimentally induced (high-salt diet) hypertension.

Chromosomal analyses are being performed in an increasing number of laboratories. Microscopically observable chromosomal defects are usually associated with gross clinical abnormalities (*20*) such as the 13–15 trisomy (*21*). Tissue cultures have been used to identify genetic cellular defects in relatives of patients with Hurler's syndrome (*22*). The significance of nonchromosomal heredity in the field of human genetics has not been established (*23*).

The role of Spaeth and Barber (*24*) is exemplary of the part that ophthalmology can take in this phase of disease. They discovered homocystine excretion in a mentally retarded child with dislocated lenses at a time when the disease was unreported. The patient was channeled to the National Institutes of Health, where the specific enzymatic defect was elucidated (no hepatic cystathionine synthetase activity (*25*)). The enzymatic levels of the heterozygous carriers (the parents) were later reported to be about 40 percent of the normal value (*10*). This type of collaborative approach to systemic disease and the eye has frequently been the most rewarding.

2. *Environmental Factors.*—The environment has a significant influence on disease states. Pathologic processes may be induced or prevented by alterations of the environment. The incidence of retrolental fibroplasia has been drastically reduced in premature infants by curtailing the use of oxygen-enriched breathing mixtures (*26*). Thalidomide administered during pregnancy has induced choroidal colobomas (*27*). Chloroquine has produced retinopathy and keratopathy (*28*), while MER-29 (triparanol) (*29*) and corticosteroids (*30*) have caused cataracts.

New drugs are continually being produced. Each medication alters the internal milieu of the orgaism. Both beneficial and harmful effects of these drugs must be assessed on each system of the body, including the eye. At times, the therapeutic benefits of certain pharmacological products must wait years to be recognized. On the other hand, toxic effects may be brought to light initially in a clinical situation when the drug has already been marketed, with later demonstration of its animal toxicity (*31*). Where ophthalmology is concerned, it seems that a limited number of large laboratories devoted to these aspects of pharmacologically induced environmental changes, and working in conjunction with clinical ophthalmic pharmacologists, would be a more practical and efficient method of dealing with these problems.

Removal of part of the normal environment, e.g., lactose products in galactosemia and phenylalanine in phenylketonuria, may prevent the disease from becoming fully manifest.

The epidemiology of diseases affecting the eye needs further elucidation. In TRIC viral infections, a group of English investigators (*32–35*) has shown that there is clinically recognizable pathology in the cervix and abnormal cervical and urethral cytology (occasionally with inclusion bodies). The male urethra may harbor the organism. Some of the adults in this study were parents of infants who had de-

veloped TRIC ocular infections. The epidemiology of toxoplasmosis uveitis is not understood (*36*). There remains considerable disagreement about the mother's ability to infect repeated offspring in utero (*37*). A greater understanding of the epidemiology of disease is necessary before successful measures can be applied. Thus, eradication of a TRIC viral infection in the mother is far superior medically to later treatment of the infected infant. Vaccines have proven their worth in certain infectious diseases but are relatively undeveloped in ocular infections.

Stage II: Preclinical Disease

In this phase of disease, the individual is asymptomatic. He may be in a remission or may never develop a manifest illness. If the process could be discovered during this quiescent state, it could possibly be "cured" or at least held in abeyance. The fundamental problems at this stage are detection of the disease and elucidation of the factors which bring the disease to a clinical state.

Detection of stage II lies in physical examination and special laboratory tests. Disease latent elsewhere in the body may manifest itself in the eye. Poor correlation has been found between the presence of arcus senilis and ischemic heart disease (*38, 39*). Serum cholesterol was found to be higher in those individuals with arcus, but this relationship reached a significant level only in the age group from 40 to 49 (*39*). Arcus, however, might be better correlated with different parameters, such as the amount of atherosclerosis found at autopsy.

Retinal blood-vessel constriction on breathing oxygen has been shown to correlate with the increase of cerebral blood flow induced by breathing 5 percent CO_2 (*40*). Loss of this retinal vessel reactivity might be related to cerebral arteriosclerosis. Electrooculogram and electroretinogram abnormalities have proven too variable for the purpose of elucidating the toxic effects of chloroquine prior to the development of observable retinopathy (*41*). Ophthalmodynamometry could be employed to diagnose asymptomatic carotid occlusive disease.

Drugs can be used to bring out underlying disease. Hydralazine therapy may produce a clinical picture resembling systemic lupus erythematosis in patients with underlying lupus diathesis (*42*). It is not known whether drug-induced clinical syndromes carry the risk of irreversibility or of changing the ultimate prognosis. Even when disease can be detected in this preclinical state, the value of therapy has not been ascertained. Which patients in stage II of a disease will proceed to stage III has not been clarified.

Another problem related to this phase of illness is that only in certain individuals do particular structures such as the eye become involved in active disease occurring elsewhere in the body. Only 10 to 16 percent of patients with ankylosing spondylitis develop iritis (*43*). It has been stated that, in adult Coats's disease, evidence of previous uveitic disease must exist in order for the manifest disease to be produced in the presence of increased serum lipid levels (*44*).

In quiescent disease, the factors responsible for exacerbation need further elaboration. In herpes simplex, for example, numerous external factors have been incriminated. Experimentally, allergic reactions (*45*) and adrenalin administration (*46*) can arouse the dormant infection. It is not known whether all these stimuli produce their effect through a common physiologic mechanism. The question of the locale of the inactive herpes virus particles is not settled (*47*).

Stage III: Clinical Disease

A large part of clinical and animal experimentation has been devoted to the overt phase of disease. Well-described clinical and laboratory observations in a particular disease and comparisons of various disorders have always been of value. From such material, questions can be raised and theories formulated which form the basis of future investigation.

The eye has been used often for diagnostic purposes. The finding of a Kayser-Fleisher ring in Wilson's disease or of band keratopathy in hypercalcemia has helped to establish correct diagnoses. Recently, the Mecholyl test has proven of value in familial dysautonomia (*48*). Symptomatic sickle cell disease can apparently be diagnosed from a characteristic pattern of conjunctival vessels (*49*). Raynaud's disease must be added to those disorders associated with serum hyperviscosity and its characteristic ophthalmoscopic picture (*50*).

New techniques for examining the eye have been helpful in making early diagnoses. Fluorescein injections have proven useful in the diagnosis of early papilledema and in differentiating it from pseudopapilledema (*51*). These are a few of the newer diagnostic signs and tests that make examination of the eye important in general medical diagnosis and evaluation.

Evaluation of the efficacy of drug therapy is essential—but only in carefully controlled studies. There is a vast amount of ophthalmic literature devoted to the description of noncontrolled evaluation programs that have "proven" the efficacy of various drugs. The drug companies, the Food and Drug Administration, and the editorial staffs of the various journals could curtail at least a part of this useless literature.

Drugs of therapeutic value have often evoked a great deal of investigational activity (e.g., 5-iododeoxyuridine (*52*)). Negative results and side effects of

drugs have often led to the development of useful products such as acetazolamide (*53*).

Laboratory investigation has been useful in infectious diseases, and the exact etiology of many "viral diseases" has been found through this source. New viruses, such as adenovirus 2 (*54*) as a cause of keratoconjunctivitis, continue to be discovered. Mimeae infections may be more prevalent than was previously assumed (*55*). The role of certain agents such as the Mycoplasma (*56, 57*) is not well understood in relation to the eye.

Autoimmune disease has come into vogue. Sjögren's syndrome, even without associated arthritis, appears to fit into this category (*58*). Diseases such as temporal arteritis should be evaluated along these lines. It has been suggested that idiopathic uveitis is an autoimmune disease, but the evidence is conflicting. Antiuveal precipitating antibodies can be found in a high percentage of patients with uveitis (*59*). However, serum factors classically associated with autoimmune disease—for example, antinuclear antibodies—are no more prevalent in uveitis patients than they are in the general population (*60*). Family studies for antiuveal antibodies have not been conducted.

In the "known" causes of uveitis, laboratory tests are at times of limited benefit. Toxoplasmosis may occur in the presence of a low (*61*) or negative (*62*) dye titer. Serum tests for Toxocara canis antigen are useful only as confirmatory evidence because of the high percentage of the population with demonstrable blood titers (*63*). The evidence of histoplasmosis and amebiasis as etiologic agents of uveitis remains circumstantial (*64*).

The pathology of human ocular disease has given insight into disease processes. The discovery of toxoplasmosis in intraocular tissue, for example, was a milestone (*65*), and the recent discovery of pars plana cysts filled with mucopolysaccharides in multiple myeloma has stimulated the clinician to look for this abnormality in vivo (*66*). Histochemical and electron microscopy are being used more frequently in examination of human ocular specimens, but a problem encountered in most institutions is the acquisition of eyes from routine autopsy cases. An attempt should be made to alter this situation.

Animal experiments lead to a better understanding of stage III disease, but these investigations have always presented the problems of species difference, methods of inducing the disease, and whether or not results can be extrapolated to man.

Lathyrism, a chemically induced counterpart of the Marfan's syndrome, has never had its ocular components fully investigated (*67*). Most workers in this field have used the rat as the experimental model. However, this is a poor choice when dislocation of the lens is being evaluated because of its large size in comparison to the rest of the eye. Animal models have been established for periarteritis (*68*) and renal hypertension (*69*).

Problems related to atherosclerosis have been investigated in the rabbit cornea (*70*). Cancer therapy has been evaluated by its influence upon tumors transplanted to the anterior chamber (*71*). Attempts to simulate the human ocular manifestations of infectious disease (toxoplasmosis (*72*), histoplasmosis (*73*), syphilis (*74*), herpes simplex (*75*) and Candida albicans (*76*)), have met with success only with certain organisms. Latex spheres injected into the retinal circulation have induced histologic changes closely resembling the "cytoid body" (*77–79*) histologically and funduscopically. Galactose-induced cataracts have been studied histologically and biochemically (*80, 81*). Rats fed diets rich in homocystine manifested multiple abnormalities (*82*), but the intraocular structures were not specifically noted, and again, this animal was a poor choice for ophthalmic investigation.

Diseased animals may make excellent experimental models for the study of the details of disease. Fresh specimens become available for biochemical, histochemical, and electron microscopic analyses, and drug therapy can be evaluated under a more controlled situation than is possible in human disease.

Spontaneous disease in animals has been used only to a limited extent (*83*). Tissue cultures permit even more exact control of environmental conditions. Bornstein has demonstrated demyelinatization of neurons grown in tissue culture when the culture is bathed with sera from active multiple sclerosis patients (*84*). The technique has been used extensively in virology, but little use has been made of it in studying pathologic tissue in culture.

Stage IV: The Postdisease State

Unfortunately, when disease of the eye has been cured, opacification of the various refractive media or retinal destruction frequently leads to diminished vision. Treatment today may be removal of the damaged structure (lens), replacement of opacified tissue (cornea, vitreous), or the use of low-vision aids. The main social and psychological problems encountered in persons with poor vision have been dealt with at length (*85, 86*). This group of patients has been used in studies of the persistence of antibody response (*87*).

With improvements in the treatment of active disease, patients in stage IV will have less residual damage.

Conclusions

Investigative ophthalmology has made rapid strides in the past several decades. This review has

outlined a few aspects of systemic diseases involving the eye which require further study. Whereas most research activity has taken place in stage III (the active clinical phase of the disease), stage I (the predisease state), and stage II (the preclinical disease state) represent areas of research from which the greatest benefits may be derived. Proper financing of projects and the inducement of the appropriate scientific personnel into the field are necessary for further advances.

RECOMMENDATIONS

It is recommended that the following categories of projects be fully supported.

Genetic Influences in Systemic Disease and the Eye

1. *Statistical Methods.*—Studies are needed to evaluate whether individuals with certain genetic markers are more susceptible to ocular disease; e.g., uveitis in sarcoidosis, with or without a concomitant hemoglobinopathy.

2. *Laboratory Tests and Physical Diagnostic Methods.*—New clinical and laboratory methods are needed for detecting the carrier state and preclinical genetic disease. Thus support of chromosomal laboratories is urged.

3. *Twins.*—Studies of fraternal and identical twins in relation to eye disease are needed.

4. *Experimental Animal and Tissue Culture Models.*—Experimental attempts to produce such models are important in our ultimate understanding of genetic influences. Animals with spontaneously occurring disease states (diabetes, Hunter-Hurler-like disease) should be collected and bred for biochemical, histologic, and pharmacologic investigations.

Environmental Influences in Eye Disease

1. *Epidemiology.*—Ocular diseases such as trachoma, onchocerciasis, and toxoplasmosis should be thoroughly investigated epidemiologically, with the aim of their widespread eradication.

2. *Ophthalmic Consultant to Epidemiologic Teams.*—Teams studying sudden outbreaks of a disease (e.g., histoplasmosis) where large segments of a community are primarily infected should include an ophthalmologist. Information, otherwise unavailable, would become available.

3. *Pharmacologic Centers.*—Centers should be established for both animal ocular investigation of new, interesting drugs and for human clinical investigation (efficacy, side effects, toxicology, etc.). Such centers would work in close association with each other, the Food and Drug Administration, and the drug companies. Funds should be available for training individuals interested in ocular pharmacology.

Preclinical Disease

1. *Correlative Studies.*—Studies demonstrating a relationship between ocular signs and systemic disease or ocular disease with both biochemical abnormalities and systemic disease are needed.

2. *New Diagnostic Techniques.*—Such techniques are essential for evaluating asymptomatic disease. If the ophthalmic artery pressures were measured (ophthalmodynamometry) in every individual over a specified age, would finding a difference in the ophthalmic artery pressure of the two eyes in an asymptomatic individual help to prognosticate the ultimate development of a carotid artery occlusion or a stroke?

3. *Factors Affecting the Eye in Systemic Disease.*—Continued investigation should be supported into those components of systemic disease which prevent, ameliorate, initiate, or aggravate concomitant ocular involvement.

Clinical Disease

1. *Dissemination of Knowledge.*—The importance of ophthalmology in evaluating general medical diseases should be widely taught both to general practitioners and internists, and to other ophthalmologists.

2. *Experimental Models.*—As in genetic disease, full support is needed for establishing experimental animal and tissue-culture models.

3. *Clinical Investigations.*—Full immunologic, biochemical, histochemical, microscopic, and electron microscopic studies on human serum and biopsy material continue to need further exploration and will undoubtedly provide some of the most pertinent information.

Postdisease State

1. *Transplantation Experiments.*—Work should continue along the present lines of investigation with perhaps more studies on central nervous system regeneration and the use of hyperbaric oxygen in the survival of whole organ transplants.

2. *Data Collection.*—Accurate methods and widespread programs should be used to code causes of blindness and visual loss. Only in this way can we arrive at an accurate assessment of the progress made over many years in combating the various causes of blindness. It is also a method of detecting previously unknown factors leading to visual loss.

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Appendix A.—*Infective diseases*

Infection	Ocular tissue involved	Present therapy
Fungi:		
Actinomycosis	Lids, lacrimal gland, sac Canaliculi Conjunctiva Cornea Uvea Retina Orbit	Sulfonamide. Penicillin. Amphotericin. (1).
Aspergillosis	Conjunctiva, canaliculi Cornea Sclera Uvea Orbit	Iodides. Penicillin. Amphotericin. (1).
Blastomycosis	Lids, lacrimal sac Conjunctiva Cornea Uvea	"
Coccidiodomycosis	Lids Orbit	" " " (1).
Cysticercosis	Lids Orbit Uvea Retina Optic nerve	(2).
Monilia	Lids, conjunctiva Orbit Cornea, uvea	Amphotericin. Gentian violet. Nystatin. (1).
Bacteria:		
Anthrax	Lids Orbit	Antibiotics. Sulfonamides.
Brucellosis	Conjunctiva Cornea Uvea Optic nerve Retina, vitreous Extraocular muscles	" (1).
Chancroid (Hemophilus ducreyi)	Lids Conjunctiva Cornea	Sulfonamides.
Cholera	Lids Conjunctiva, cornea Uvea	Chloramphenicol. (3).
Diphtheria	Lids Conjunctiva Cornea Orbit Lacrimal sac, gland Retina Extraocular muscles	Penicillin. Antitoxin.
Dysentery	Conjunctiva, cornea Uvea Retina	Sulfonamides.
Erysipelas	Lids, conjunctiva, cornea Lacrimal gland	Antibiotics.
Gonorrhea	Conjunctiva, cornea Uvea Retina Lacrimal gland	Penicillin.
Granuloma venereum	Lids Cornea	Antibiotics.
Leprosy	All ocular tissues	Sulfones. Antibiotics for secondary infection.
Leptospirosis (Weil's disease)	Lids, conjunctiva, cornea Uvea, retina	Antibiotics. (2).
Pertussis	Lids, conjunctiva, retina External and internal ocular muscles Orbit	Nonspecific.
Plague (B. pestis)	Lids, cornea, orbit Uvea	Sulfonamides and antibiotics. Antiserum.
Scarlet Fever	Lids, cornea, uvea Optic nerve Ocular muscles	Antibiotics.
Septicemia (bacterial) (other organisms as well).	Lids, cornea Uvea, retina Orbit, optic nerve Lacrimal gland	"
Syphilis	All ocular structures	Penicillin. Arsenicals, bismuth, Mercury. Fever, steroids.
Tuberculosis	All ocular structures	Streptomycin, isoniazide, PASA.
Tularemia	Lids, cornea, conjunctiva Orbit, optic nerve	Streptomycin.

[1] Often inadequate.
[2] Unsatisfactory.
[3] Supportive.

Appendix A.—*Continued*

Infection	Ocular tissue involved	Present therapy
Typhoid	Lids, lacrimal gland Orbit Uvea, retina, optic nerve Ocular muscles	Chlorampbenicol. (3).
Virus:		
Cytomegalic inclusion	Uvea, retina	(2).
Dengue	Lids, conjunctiva, cornea Uvea, Optic Ocular muscles	(2).
Herpes simplex	Lids, conjunctiva, cornea Uvea	I.D.U. Cytosine arabinoside. Cauterization. Mechanical debridement. (2).
Herpes zoster	Lids, conjunctiva, cornea, uvea Ocular muscles, optic nerve	(2). Nonspecific.
Influenza	Conjunctiva, cornea Uvea, retina Optic nerve Ocular muscles	(2).
Lymphogranuloma venereum	Lids, sclera, uvea Optic nerve	Sulfonamides. Aureomycin.
Adenovirus	Conjunctiva Cornea	No specific therapy.
Mumps	Conjunctiva, lacrimal gland Cornea, sclera, uvea Optic nerve	
Newcastle's disease	Conjunctiva	(2).
Poliomyelitis	Ocular muscles Optic nerve	Prophylactic vaccine. Nonspecific therapy. (2).
Rickettsial diseases	Lids Uvea, retina Orbit	
Rubella	Congenital deformities Globe Retina and choroid Lens	(2).
Trachoma	Lens, conjunctiva, cornea	Antibiotics, sulfonamides.
Typhus (R. Prowazekia)	Lids, conjunctiva, lacrimal gland Orbit Retina Optic nerve	Antibiotics.
Vaccinia	Lids, conjunctiva, cornea Orbit	I.D.U.—Hyperimmune sera.
Varicella	Lids, conjunctiva, cornea Optic nerve	Nonspecific.
Variola	Lids, conjunctiva, cornea, lacrimal apparatus. Uvea, retina	I.D.U. (2).
?Cat-scratch fever	Lids, conjunctiva	No specific therapy.
?Microplasma (Reiter's syndrome) (might be classed under Collagen disease).	Uvea, conjunctiva Cornea	Steroids.
?Behcet's disease (might be classed under noninfectious disease).	Uvea, conjunctiva Cornea	"
Protozoan and parasitic diseases:		
Amoebiasis	Conjunctiva, sclera, uvea, retina	Sulfonamide, amoebecidal agents. (2).
Anklyostomiasis	Conjunctiva Retina Optic nerve Ocular muscle	Carbon tetrachloride.
Ascariasis	Lids, conjunctiva Uvea, retina	"
Cysticercosis	All ocular structures	(2).
Echinococcosis	Conjunctiva, orbit	(2).
Filariasis	Lid, orbit, conjunctiva, cornea Uvea, retina	(2).
Leishmaniasis	Conjunctiva Cornea	Antimony. (2).
Malaria	Lids, conjunctiva, cornea Orbit, uvea, retina Optic nerve Ocular muscles	Antimalarial—quinine, chloroquine, primaquine, atebrin, etc. (not completely satisfactory).
Onchocerciasis	Lids, orbit, anterior chamber Papilledema Cornea	Hetrazan, Suramin.
Schistosomiasis	Lids, conjunctiva	Antimony.[2]
Toxoplasmosis	Retina Uvea (secondarily)	Daraprim, sulfonamides, steroids. (2).
Trichinosis	Conjunctiva, orbit, muscles	Triabendazole (probably inadequate).
Visceral larval migrans (Toxocara)	Uvea, retina	(2).

[1] Often inadequate.
[2] Unsatisfactory.
[3] Supportive.

Disorder	Ocular tissue involved	Present therapy
Blood dyscrasia:		
Anemias	Lids, conjunctiva, retina, optic nerve	
Aplastic		(1).
Hypochromic		Replacement therapy.
Pernicious		"
Secondary		"
Sickle cell disease	Lids, conjunctiva, retina	Nonspecific.
Hemophilia	Lids, orbit, conjunctiva, uvea, retina	Transfusion.
Hodgkin's disease	Lids, lacrimal gland, orbit, uvea (?)	Chemotherapy.
Brill-Symmers disease	Lids, lacrimal apparatus, orbit	"
Hypergammaglobulinemia	Conjunctiva, retina	Remove cause (e.g., drug).
Leukemia	Lids, conjunctiva, lacrimal apparatus	Chemotherapy.
Polycythemia	Uvea, retina, orbit	
	Lids, conjunctiva, retina, optic nerve	P(32), Chemotherapy.
Purpura	Lids, conjunctiva, retina, uvea	Remove allergic agent.
		Surgery.
Lipidoses:		
Hurler's disease	Orbit, cornea	(2).
Gaucher disease	Lids, conjunctiva, cornea	Chemotherapy.
Niemann-Pick disease	Sclera, uvea, retina	(2).
Tay-Sachs disease	Retina	(2).
Batten-Mayou disease		(2).
Spielmeyer-Vogt disease		
Endocrine dysfunctions		
Adrenals:	Lids, conjunctiva, orbit	Plasmapheresis, chemotherapy.
Hypo	Lids, brows, lashes	Replacement.
Hyper	Retina	Surgery.
	Orbit	Adrenergic blockade.
Pituitary		
Hypo	Pupillary reactions, retina	Hormonal.
Hyper	Orbit, chiasm, nerve	Replacement.
		Surgery.
		Destruction—X-ray proton beam.
Parathyroid:		
Hypo	Lids, lens	Replacement, surgery.
Hyper	Orbit, cornea	Surgery.
Thyroid:		
Hypo	Lids, lashes, brows, conjunctiva, cornea	Replacement.
Hyper	Lids, orbit, lacrimal apparatus	Surgery, suppressive drugs.
	Ocular muscles	Hormonal inhibition.
Collagen diseases	Lids, conjunctiva, cornea, sclera	Steroids.
Dermatomyositis		(2).
Lupus erythematosis	Uvea, retina, optic nerve	(2).
Periarteritis		
Temporal arteritis		(2).
Scleroderma	Ocular muscles	(2).
Sjögren's syndrome	Cornea, conjunctiva	(2).
Waegener's granulomatosis	Cornea	Corticosteroids.[2]
Hypertension	Conjunctiva	Antihypertensive drugs.
	Retina	Surgery (not completely satisfactory).
Myasthenia Gravis	Lids, ocular muscles	Anticholinesterase agents.[2]
Pregnancy	Retina, optic pathways, muscles	Delivery.
Osseous disorders:		
Fragilitas ossium	Sclera, cornea, lens, optic nerve	(2).
Leontiasis ossea	Orbit, lacrimal apparatus	(2).
	Optic nerve	
Paget's	Orbit, ocular muscles	(2).
	Retina, choroid	
	Cornea	
Vascular diseases:		
Arteriolar sclerosis	Retina	Treat hypertension.
Atherosclerosis	Retina, orbit, conjunctiva, uvea	Diet, hormones.
Angiomatosis	Retina	Local destruction.
Vitamin deficiencies:		
Vitamin A	Conjunctiva, cornea	Vitamin supplements.
Vitamin B	Conjunctiva, cornea, optic nerve	"
Vitamin C	Lids, conjunctiva, cornea, retina	"
Vitamin D	Lens, cornea	"
Inborn Errors of Metabolism and Hereditary Disorders:		
Albinism	Uvea, retina	(2).
Alkaptonuria, ochronosis	Cornea, sclera, conjunctiva	(2).
Amyloidosis (primary)	Retina, vitreous, uvea	(2).
	Lids, conjunctiva, sclera, ocular muscles	
Angiokeratoma (Dystopic Lipoidosis)	Cornea, conjunctiva	None.
Cystic fibrosis	Optic nerve, pupil	Antibiotics, diet.
Cystine storage disease	Conjunctiva, sclera, uvea	(2).
		Vitamin D.
Familial dysautonomia	Cornea, pupil	(1).
Galactosemia	Lens	Early detection.
		Exclusion of milk galactose foods.
Hepatolenticular degeneration	Cornea, lens	(2).
	Retina	Penicillamine.
		B.A.L. copper-free diet.
		Cation-exchange resins.
Homocystinuria	Zonules, lens	Diet(?).
	Retina	Surgery.
Hypercholesterolemia	Lids, cornea	Diet.
Hyperlipemia	Lids, retina, cornea	"
Lowe's syndrome	Cornea, lens	Surgery.
	Glaucoma	Glaucoma medications.
		Correction of electrolyte imbalance.
Marfan's syndrome	Lens, zonules, retina, angle	Surgery, glaucoma therapy.
Marchesani syndrome	Lens, zonules	Surgery.
Osteopetrosis	Optic nerve	(2).
Phacomatoses	Lids, retina, optic nerve, orbit	Surgery, light coagulation.
Porphyria	Cornea, symblepharon	Light avoidance.

[1] Supportive.
[2] Unsatisfactory.

Appendix B.—*Continued*

Disorder	Ocular tissue involved	Present therapy
Pseudoxanthoma elasticum	Macula	Phenothiazides.
	Retina	(2).
	Angioid streaks	
Ocular cutaneous:		
Acne rosacea	Conjunctiva, cornea	Diet, corticosteroids.
Atopic dermatitis	Lens	Surgery.
		Dermatologic therapy.
Incontinentia pigmenti	Optic nerve, uvea, lens, cornea	(2).
Nevoxanthogranuloma	Iris, orbit	Surgery, X-ray.
Pemphigus	Conjunctiva	Corticosteroids.
Stevens-Johnson's syndrome	Conjunctiva, cornea	Anti-inflammatory.
		Contact lenses.
Tumora:		
Metastatic	Uvea, orbit, optic nerve	Radiation.
Wilms'	Aniridia	Surgery, chemotherapy, X-ray of primary tumor.
CNS	Optic nerve	"
Miscellaneous:		
Chronic pulmonary insufficiency	Optic nerve	Pulmonary therapy.
Crouzon's and craniostenosis	"	Surgery.
	Orbit	
Demyelinating diseases	Uvea, optic nerve, pupil	(2).
Hand-Christian-Schüller syndrome	Orbit, lids	X-ray, chemotherapy.
Metachromatic leukodystrophy	Retina	(2).
Sarcoidosis	Conjunctiva, cornea, uvea, orbit	Anti-inflammatory therapy.

[1] Supportive.
[2] Unsatisfactory.

Chapter 14—DIABETIC RETINOPATHY

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INTRODUCTION

The modern treatment of diabetes mellitus strives to keep the patient symptom-free and to prevent the development of complications. The ocular complications produce considerable anxiety in the care and management of any patient. Cataracts and involvement of the intraocular vessels and retina are a threat to vision. Cataracts can often be corrected by surgery, but vascular and retinal involvements can affect vision irreparably. Diabetic retinopathy is an enigma, a frightening complication in the prolonged life of many individuals with diabetes mellitus. Blindness and disability from this cause, in diabetic individuals who would otherwise be at the prime of life, represents a major medical challenge.

Helmholtz introduced the ophthalmoscope in 1851, and Jaeger made the first suggestion of the specific nature of diabetic retinopathy in 1856 (*1*). This specificity was not accepted universally until well into the 20th century. In 1875, Leber (*2*) concluded, from a review of the literature and from his own experience, that retinal changes were the result of a combination of renal difficulties in diabetes as well as of diabetes itself. Hirschberg (*3*) stressed the specific nature of the disease as he reviewed and classified the ophthalmologic signs in 1890.

The lack of specificity of the retinopathy—that is, the necessary coexistence of hypertension, arteriosclerosis, and other metabolic changes with diabetes—was stressed by many observers (Volhard 1921 (*4*); Wagener and Wilder 1921 (*5*); and Grafe 1924 (*6*)). More recently, it has been demonstrated that diabetic retinopathy can develop without any signs of hypertension, arteriolar sclerosis, or renal disease (Gray 1931 (*7*); Wagener et al, 1934 (*8*); Waite and Beetham 1935 (*9*); Hanum 1938 (*10*); Ballentyne 1945 (*11*); Leopold et al, 1945 (*12*); Vogelius 1949 (*13*); Croom 1950 (*14*); Kornerup 1955 (*15*); Ashton 1958 (*16*); Larson 1960 (*17*); Oosterhuis 1960 (*18*)).

Hemorrhages and exudates were the essential findings described throughout these years, but as early as 1888, Nettleship (*19*) noted the existence of proliferative retinopathy and irregularity in calibre of the veins.

Very few histologic studies were made of the retina of diabetic eyes prior to 1943 (Nettleship in MacKenzie's report 1879 (*20*); Beauvieux and Pesme 1923 (*21*); Russo 1925 (*22*); Mori 1930 (*23*); Bessiere 1932 (*24*); Agatson 1940 (*25*); O'Brien and Allen 1940 (*26*); Gibson and Smith 1941 (*27*)). The very characteristic capillary microaneurysms well described and illustrated by MacKenzie and Nettleship apparently were forgotten until their rediscovery by Ballentyne and Loewenstein in 1943 (*28*). An extensive histologic literature has accumulated since this careful work. Much of this has been summarized in reviews (Aarseth 1953 (*29*); Lundback 1953 (*30*); Ashton 1958 (*16*); Larson 1960 (*17*); Leopold 1961 (*31*); Bloodworth 1963 (*32*)). By the use of the periodic acid and fuchsin sulfate staining method (PAS) introduced by Hotchkiss, McManus (*33*), and Friedenwald (1946 and 1948), Friedenwald demonstrated (*34*) (1948) aneurysms in diabetic retinopathy more effectively than previous methods had. Ashton added the injection of neoprene or India ink into excised eyes in the preparation of flat retinas for histologic study in 1949 (*35*). These studies have established diabetic retinopathy as a distinct pathological entity.

The basic structure of the retinal, choroidal, and renal small vessels as seen by electron microscopy has been described by Feeney, Spargo, Bloodworth, and others.

Feeney (*31*) noted that human retinal capillaries differ from those in other organs in having a thicker basement membrane, more closely placed pericytes, and in the adult, extensive cavitation—Swiss cheese spaces in the region where the basement membranes of the pericytes and glial cells are in apposition to each other, with dense deposits in the wall.

The basement membrane, secreted by the endothelial cells and branching pericytes, forms a continuous system and fuses with the basement membrane of the glial cells. The cross section of a retinal capillary thus consists of:

1. a continuous layer of endothelial cytoplasm;
2. a relatively thick basement membrane representing a fused endothelial pericyte basement membrane;
3. a thick basement membrane representing the fused pericyte-glial basement membrane.

The electron microscope techniques have confirmed the thickening of the basement membrane of the retinal and renal vessels of the diabetic. However, some recent studies are not as certain as earlier ones.

The venule of the human eye has almost the same construction as the capillary. The larger venule can be distinguished from the capillary only by the fact that it has collagen in its outer wall between the basement membrane and the glial cell.

INCIDENCE OF DIABETIC RETINOPATHY

Duration

The incidence of retinopathy increases with duration of the diabetes. As long ago as 1890, Hirschberg noted the frequency of retinal changes in longstanding diabetes mellitus. The statistics on frequency and duration can be realized from the data accumulated in the accompanying tables.

Age

Prior to the introduction of insulin therapy, retinopathy seemed to develop only in diabetics over the age of 40. Juvenile diabetics failed to develop retinopathy in that era because they did not live long enough. However, the frequency of retinopathy in juvenile diabetics increased in reports after 1942 (see table). It appears that the age of the patient and the age of onset of diabetes are of little importance in influencing retinopathy, as it appears in a high percentage of both juvenile and adult patients if they live long enough. Wagener, in 1934 (*16*), reported a retinopathy incidence of 17.7 percent and, in 1945, of 29.6 percent. A reevaluation today would probably lead to an even greater incidence. Control of the chemical aspects of diabetes has lead to a prolonged life for the individual, increasing his chances of ultimately developing a vascular complication such as retinopathy.

The incidence of proliferative retinopathy also increases with duration of the disease (see table). The average duration of the diabetes, before proliferative retinopathy develops, is 17 to 18 years (Root 1959) in those under 50. It may appear sooner in those over this age.

Sex

Females seem to be more prone to retinopathy than males are (Dry, T. G., and Hines, E. A. 1941 (*37*); Henisius 1950 (*38*); Taylor 1954 (*39*)), although not all studies agree on this point (Lundback 1954 (*30*), Annals of Internal Medicine; Aarseth 1953 (*29*)).

Frequency of diabetic retinopathy prior to 1940

Author	Year	Number of patients	Percent with retinopathy
Kako	1903	280	23.5
Grafe	1922	600	13.3
Andersen	1925	292	15.4
Carmidge	1930	1,000	4.8
Wagener	1934	1,052	17.7
Waite and Beetham	1935	2,002	20.2
Braun	1937	697	16.5
Hanum	1938	966	20.2

Frequency of diabetic retinopathy after 1940

Author	Year	Number of patients	Percent with retinopathy
Lee	1941	100	31
Pollack et al	1941	997	8
Wagener	1945	1,021	29.6
Ballentyne	1946	561	31.7
Hagensen	1948	188	4.8
Jackson et al	1949	75	46.6
Henisius	1950	185	16
Bjerkelund	1951	923	14
Aarseth	1953	288	42
Cowan et al	1955	500	43.2
Kornerup	1955	1,000	47

Incidence of retinopathathy in juvenile diabetics

Author	Year	Percent with retinopathy
O'Brien and Allen	1942	4
White and Waskow	1948	45
Walker	1950	46
Post and Stickle	1951	74

Incidence of proliferative retinopathy

Author	Year	Percent with retinopathy
Wagener et al	1934	0.8
Hanum	1938	1.2
Lundback	1953	6.3
Engleson	1954	6.9
Kornerup	1958	8.4
White (15 years duration)	1959	18.0
White (30 years duration)	1959	59.0

Author	Year	Years of duration	Percent with retinopathy
Waite and Beetham	1935	1.0	5.7
		1 to 1.9	10.7
		2 to 2.9	11.8
		3 to 4.9	13.8
		5 to 9.9	20.5
		10 to 15	43.0
		Over 15	58.9
Hanum	1939	Under 2	11.0
		2 to 4	14.0
		5 to 9	24.0
		10 to 20	48.0
		20 plus	3.0
White	1949	20 plus	93.0
	1960		
Jamieson and Nichols	1950	15 plus	65.0
Root et al	1950	Under 10	4.0
		10 to 19	50.0
		20 to 29	60.0
Cowan et al	1955	Under 10	28.0
		10 to 15	45.0
		Over 15	61.5
Kornerup		Whole group.	47.0
		15 plus	83.0

Other causes of retinal microaneurysms

Disease	Authors	Year
Retinal venous occlusion	Loewenstein and Garrows.	1945
"	Ballentyne and Michaelson.	1947
"	Becker and Post	1951
"	Ashton	1951
"	Wise	1956
Eales's disease	Becker and Post	1957
"	Wise	1956
Thrombotic glaucoma	Ashton	1951
Chronic glaucoma	"	1957
Secondary glaucoma	"	1957
Malignant hypertension	Friedenwald	1957
"	Wexler and Branowern	1950
Arteriosclerosis	Hartford	1953
Hypochromic anemia	Friedenwald	1950
Pernicious anemia	Becker	1952
Sickle cell anemia	Edington and Sarkies	1952
Pulseless disease		
Hemachromatosis	Hudson	1953
Total pancreatectomy	Burton et al	1957

COURSE OF RETINOPATHY

Stages

Ballentyne, in 1944 (*40*), divided retinopathy into five stages. The first included microaneurysms, with or without punctate hemorrhages and minute exudates. The second stage revealed dot- and blot-like hemorrhages and waxy exudates. Periphlebitis, phlebosclerosis, large hemorrhages (intraretinal and preretinal and vitreal), enlarged vascular channels, new vessels in the vitreous, and early retinitis proliferans came in the third stage. These changes advanced in the fourth and fifth stages and included retinal detachment and other degenerative complications.

Other classifications have been suggested (Scott 1953 (*41*); Jensen 1955 (*42*)). Scott stressed the early appearance of venous changes in some eyes, and the occasional rapid advance from the stage of venous changes and microaneurysms directly to the proliferative stage, characterized by newly formed vessels and glial tissue proliferation.

Not all patients advance at the same rate, and spontaneous remissions have been noted. Usually the progression of the retinopathy is slow, but spurts occur. Initially only one eye may show the changes, but the disease is usually bilateral, although the two eyes may differ in degree of involvement at any one time. The retinopathy may progress, then stop and not change for years; and complete disappearance has occurred, though very rarely.

Visual Acuity

Visual disturbance will depend on degree of involvement of the macula. Retinopathy can be present for years without significant disturbance of vision. However, exudates and hemorrhages can occur in the macula early and reduce visual acuity. Proliferative change with associated glial and fibrous tissue usually produces vision-impairing change. The prognosis for retention of vision is difficult to determine once retinopathy appears, but progressive loss is the rule. Once proliferative changes occur, the prognosis must be guarded. The chances of deterioration are greater the older the patient is at the time of first diagnosis, and somewhat greater in eyes with hemorrhages and/or exudates than in those with microaneurysms alone (Caird and Garrett 1963 (*43*)).

Ophthalmoscopic Appearance

1. *Optic Nerve.*—The optic nerve is not involved in early diabetic retinopathy. In complicating diseases such as hypertension, renal disease, central retinal vein occlusions, and intracranial space-taking lesions can produce edema of the nerve head, as in nondiabetics. New vessels may form on the nerve head in diabetics during the proliferative stage of retinopathy.

2. *Macula.*—There has been discussion of pigmentary changes in the macula of diabetics (Jensen and Lundback 1955 (*42*)). However, such changes are not specific (Larsen 1960 (*17*)).

3. *Venous Changes.*—Generalized dilatation and fullness of the retinal veins have been described as early changes in fundi of patients with diabetes mellitus who have no other signs of vascular involvement (Wagener et al., 1945 (*8*); Mylius 1937 (*44*); Ballentyne and Lowenstein 1943 (*11*); Harden 1956 (*45*) and Ashton 1958 (*16*)). As the retinopathy progresses, other venous alterations are noted. These changes may infrequently precede microaneurysm appearance. These include beading, tortuosity, localized constrictions, varicosities, nodular and aneurysmal dilatations, and sheathing (O'Brien and Allen 1940 (*26*); Gibson and Smith 1941 (*27*); Wagener 1945 (*8*) and Scott 1953 (*4*)). Central or branch retinal vein occlusion is a frequent finding in diabetics. This occurs in juvenile diabetes of longstanding (Ditzel and White 1957 (*46*)) as well as in older diabetics.

Other diseases may produce these pronounced retinal vein changes—for example, Eales's disease, tuberculous periphlebitis, lupus erythematosus, macroglobulinemia, and sickle cell anemia. Sheathing has been described in multiple sclerosis by Rucker in 1945 (*16*).

4. *Retinal Arteries.*—The retinal arteries are usually normal in juvenile diabetics who develop retinopathy. In the older age groups with longstanding disease, evidence of hypertension, arteriolar sclerosis, and arteriosclerosis is frequent.

5. *Retinal Microaneurysms.*—Retinal microaneurysms may be visualized as pinpoint or punctate hemorrhages. These are usually scattered throughout the posterior pole or in and around the macular area. They appear as small, round, distinctly outlined dark red spots. Their size may vary. They may

be differentiated from deep punctate hemorrhages by their persistence. Retinal hemorrhages may disappear rapidly, in a few weeks. Microaneurysms may also disappear, but slowly. Usually, they persist and increase in numbers.

Retinal microaneurysms can occur in other diseases (see table). Those associated with venous closures are usually about the obstructed vein. The other diseases usually show only a few microaneurysms, and these are not located in the posterior pole.

6. *Retinal Hemorrhages.*—The retinal hemorrhages most characteristic of diabetes are deep, round, red, and localized in the posterior pole. In the earliest stages, they are difficult to distinguish from microaneurysms. As the retinopathy progresses, the hemorrhages increase in number and size. Superficial hemorrhages appear in the later stages. These are seen in a variety of diseases—for example, in hypertension, blood dyscrasias, papilledema, and thrombosis of retinal veins. The older the patient at the time of onset of the retinopathy, the earlier the superficial hemorrhages appear.

7. *Retinal Exudates.*—The characteristic retinal exudates of diabetes are hard looking, and white or yellowish white. Circinate exudates, coalescing white exudates distributed in the course of the major vessel surrounding the posterior pole, are also found frequently in diabetic fundi, but they are seen in Coats's disease, senile macular degeneration, and venous thrombosis as well. The hard, white, small exudates are seen early. They usually follow the microaneurysms but may precede them.

The "cotton-wool" type of exudate is seen in diabetic retinopathy when it is complicated by hypertension or renal disease.

8. *Preretinal, Subhyaloid Hemorrhages.*—Late in the course of the retinopathy, hemorrhages of varying sizes may develop suddenly. They are superficial and are held to the retina by the internal limiting and the hyaloid membranes. Often they assume a boat shape. Some are absorbed promptly in the course of several weeks. Others require months to disappear. Occasionally they break into the vitreous. Visual disturbance will depend on their place in the retina. Other conditions, such as trauma and subarachnoid and subdural hemorrhages, may produce preretinal hemorrhages.

9. *Vitreous Hemorrhage.*—Vitreous hemorrhage usually is sudden in onset and precedes or follows the development of proliferative retinopathy. It is always associated with a reduction in vision. Absorption is usually prompt but sometimes delayed for months. The persistent hemorrhage is usually followed by newly formed vessels and fibrous tissue. With recurrent vitreous hemorrhages, absorption is slower and complications, for example, fibrous tissue, retinitis proliferans, and glaucoma, more frequent.

The hemorrhages appear as a haze, ophthalmoscopically, or there may be a red or black reflex. Fundus details may be seen hazily or be obscured. As the hemorrhage absorbs, the blood tends to clot and form vitreous floaters or masses that can be seen to move about as the eye is rotated.

Other conditions may also produce vitreous hemorrhages (e.g., Eales's disease, retinal tears, venous thrombosis, infections, and trauma).

Vitreous detachment, partial or complete, can follow vitreous hemorrhage and proliferative retinopathy.

10. *Proliferative Retinopathy.*—This is characterized by newly formed vessels extending toward and into the vitreous, with accompanying membrane formation. The new vessels may move about like tufts or water weeds and appear to be held together by a fine veil. They usually follow vitreous hemorrhages. As the organized tissue shrinks, it may give rise to a retinal tear and subsequent detachment. Proliferative retinopathy can be seen in Eales's disease and in late stages of venous thrombosis, sickle cell anemia, and pulseless disease.

It is difficult to distinguish between new vessel formation in the retina and dilatation and hypertrophy of preexisting retinal capillaries.

Preretinal, newly formed vessels are considered to be true neovascularization. These, as well as fibrous tissue, may form anywhere in the fundus. The fibrous tissue is usually preceded by new vessel formation but occasionally may occur first.

Root and his coworkers demonstrated in 1959 (*36*) that proliferative diabetic retinopathy is seen more frequently in the juvenile and middle age groups. Older patients develop this complication in a shorter time but less frequently. The average duration of diabetes before the appearance of retinal complications is 15 years in the juvenile and middle age groups.

Usually, but not inevitably, retinitis proliferans is an indicator of ensuing serious visual loss. Retinal detachment, hemorrhagic glaucoma, and rubeosis irides are frequent subsequent findings.

RELATIONSHIP OF DIABETIC RETINOPATHY TO OTHER DIABETIC COMPLICATIONS

Renal Complications

The early stages of retinopathy may or may not be associated with glomerulosclerosis; the severe forms of retinopathy are almost always associated with nodular glomerulosclerosis. Diabetic retinopathy is found at autopsy in almost every patient with Kimmelstiel-Wilson renal lesions.

Correlation with other forms of renal disease in the diabetic, for example, diffuse glomerulosclerosis and exudative lesions, is not as clear cut.

Cardiovascular Complications

The characteristic microangiopathy of diabetes mellitus tends to increase with advancing cardiovascular complications—coronary artery disease, hypertension, and cerebral vascular accidents.

Neuropathy

Retinopathy is frequently present when neuropathy develops and is much more frequent in diabetics with neuropathy than in those without it. The data (Fagerberg 1959 (*47*)) suggest that diabetic neuropathy is caused by a diabetic angiopathy.

Conjunctiva

The conjunctival vessels may show widening of calibre, tortuosity, alteration in the a/v ratio, reduction in linear velocity of blood flow, aggregation of formed elements, and perivascular edema. Rees and coworkers (1961 (*48*)), following the lead of Ditzel and associates and others, believe that these changes occur more frequently in prediabetics and diabetics than in the normal nondiabetic. No definite correlation has been made between retinal and conjunctival vascular alterations. Certainly the aneurysms seen in the conjunctiva differ from those involving the retina.

HISTOPATHOLOGY AND PATHOGENESIS

Site of Lesion

The capillaries of the retina consist of two layers, except at the posterior pole, where three layers are evident. The superficial one lies at the ganglion cell layer, under the nerve fibers, and the deeper one resides in the outer molecular layer of the retina. It is the deeper plexus that shows the earliest change, the characteristic diabetic microaneurysm. Most investigators favor capillary degeneration as the initial incident in diabetic retinopathy and postulate that the capillary disease seen here is part of a bodywide microangiopathy. These capillaries have endothelial cells and intramural pericytes (mural cells). They have a common basement membrane.

Microaneurysms

The microaneurysms well described and illustrated by MacKenzie and Nettleship in 1877 (*19*) were redescribed by Ballentyne, and Ballentyne and Lowenstein, in 1943 (*28*). Microscopically, they are spherical or ovoid distensions usually 20 to 30 microns in diameter, but they may reach 70 to 100 microns. They are situated in the posterior pole, between the upper and lower temporal vascular branches on the venous side of the capillary network, in the inner nuclear layer. Initially, the microaneurysms appear as capillary dilatations. Sometimes they undergo thrombosis, or show a multiple reduplication of the basement membrane, or proliferation of endothelial cells within the aneurysm. The microaneurysm appears to develop from a dilated capillary. Other capillaries in the area may show degeneration, with disappearance of all elements except the basement membrane.

Exudates

1. "Cotton-wool" patches are not characteristic of diabetes, but are made up of fibrinous material and may involve the entire thickness of the retina or be localized in the superficial layers. The latter type involves the nerve fibers, which are swollen and contain a cell-like eosinophilic globule. Friedenwald, in 1947 (*34*) suggested that these are minute infarcts.

2. In the intermolecular or nuclear layer, one may find homogenous changes composed of albuminous or hyaline material, staining pink with hemotoxylin-eosin and surrounded by a zone of fatty material.

3. Rounded globules in the internal nuclear layer contain fat. These may be obliterated microaneurysms. The exact chemical nature of these exudates is not known.

Electron Microscopic Appearance

The outstanding characteristic of the capillary studies is the thickening of the basement membrane. This may be irregular and show reduplication. The change is a diffuse one, seems to involve all capillaries of the retina, and may precede the development of clinical diabetes and be present prior to the development of microaneurysms.

Pathogenesis

Cogan and Kuwabara (*49*) have stressed that one of the earliest histologic changes in diabetic retinopathy seen by light microscopy is "ghosting" of the mural cell.

They believe that these cells may control tonus of the capillaries. When these cells have been lost and the endothelial cells preserved, the capillary dilates as it fills with blood. This constitutes the shunt vessel. The adjacent capillaries usually show no blood and no cells—only basement membrane—and they appear atrophic. Microaneurysms develop from the lumen of the shunt vessels.

Chemical Nature of the Basement Membrane

Lazarow (*50*) has continued to study the chemical composition of the basement membrane. Comparative studies of carbohydrates and amino acid–glycoproteins revealed no difference between normal and diabetic basement membranes. Both appear to be essentially collagen. Small amounts of other proteins may be present. Lazarow has suggested that the thickening of the basement membrane through many of the capillaries of the body may be due to altered synthesis and turnover rate of this membrane.

Immunologic Nature of Basement Membrane

Blumenthal and coworkers, at the 21st Annual Diabetic Association Meeting in June 1961 (*51*), demonstrated a binding of fluorescent insulin by nodular glomerular lesions of diabetic nephropathy. The binding appeared to be specific for Kimmelstiel-Wilson lesions and could be blocked by pretreatment of the sections with insulin.

Becker and associates (*52*) confirmed the findings of Blumenthal for kidney sections and demonstrated similar binding of fluorescent insulin in retinal lesions, as well as in basement membranes of the ciliary body and the iris of the diabetic eye. This suggests an immunogenic reaction as a possible contribution to the vascular complication.

DIABETIC RETINOPATHY AND INSULIN ANTAGONISM

The role of so-called insulin antagonism or insulin binding in the development of vascular complications in the diabetic is under scrutiny at present.

The use of the rat diaphragm technique of Gemmill (1941 (*1*)) and the immunoassay insulin methods of Yalow and Berson (*53*) have demonstrated the necessity of considering pancreatic and extrapancreatic factors in discussing the effectiveness of insulin. These possibilities may be summarized as follows:

1. Overall insulin production is normal, but secretion might be inappropriate at times, resulting in inadequate levels when needed.
2. Insulin may be secreted in normal amounts but in abnormal form.
3. Insulin antagonists may be present. These could be functional, or actually interact with the insulin molecule.
4. Insulin may be secreted normally but deactivated at an abnormally rapid rate.
5. Insulin might remain ineffective as a result of a change occurring at the insulin reactive site of tissues sensitive to insulin.

It is apparent at the moment that the terms "free insulin," "inactive insulin complex," "insulin antagonist," and "atypical insulin" require clarification. Correlation of these factors and retinopathy requires investigation.

EXPERIMENTAL PRODUCTION OF RETINOPATHY

No worker has succeeded in producing retinopathy in the laboratory animal which can be accepted as exactly analogous to that seen in human diabetics. Perhaps the retinopathy described recently by Hausler in a pituitary-induced diabetic dog may fulfill the criteria (*54*); this animal had had pituitary diabetes for over 10 years. Hausler also observed retinal microangiopathy in a diabetic Chinese hamster. Bloodworth and Engerman (*55*) have produced diabetic retinopathy in the alloxan diabetic dog that also received somatotropic hormone. Retinopathy comparable to that seen in human diabetic patients was present in each of three dogs (one with alloxan-induced and two with growth-hormone-induced diabetes) which had been diabetic for over 4 years. Patz (*56*) has described retinopathy in a dog with spontaneously occurring diabetes mellitus; the diabetes had existed for over 10 years. Intraocular nonspecific hemorrhages have been produced by a variety of methods—large doses of glucose, choline-deficient diets, and alloxan—but the characteristic microaneurysms have not been seen after these methods or those which repeatedly induce characteristic renal lesions. Induced retinal vein occlusion has produced microaneurysms.

Changes similar to those seen in diabetes mellitus can be produced in the ocular vessels by induced allergic reactions (Berken (*57*), Mutlu, and Leopold (*58*)). These changes are not specific for any one antigen; they could be secondary to venous congestion and they have also been produced by toxic agents such as cobalt.

THERAPY OF DIABETIC RETINOPATHY

Attempts have been made to halt the progressive lessening of insulin production to protect the pancreatic islets. This has been done by dietary regimens plus the use of sulfonylureas that may produce hyperplasia of islet cells. Oral hypoglycemic agents work by stimulating the islet to produce more insulin, an essentially physiologic mechanism.

The exact mode of action of the diguanides is not known. They will lower blood-sugar levels in pancreatectomized animals.

The goal is to develop a long-term program that will endure for the remainder of the patient's life. It strives to keep the patient symptom-free and to

prevent the development of complications. The symptoms are usually due to high blood-sugar levels and usually respond when these levels are stabilized in a controlled range.

Prematurity onset diabetes is characterized by the absence of circulating insulin and little or no insulin in the pancreas, where the beta cell reserve is completely exhausted. Each patient must be treated with insulin.

The complications of diabetes management have shifted in importance in the past two decades. Ketosis and coma are now rare, and infections usually respond to antibiotics. The crippling and killing complications are arterial disease, neuropathy, ulcerations of the feet, nephropathy, and retinopathy. The reasons for these complications remain unknown and, therefore, specific steps for prevention cannot be taken.

Therapy at present is disappointing, inadequate, and consists of that which is contributed by the metabolic expert and by the ophthalmologist. The visible ocular complications are late manifestations of the underlying process.

At present, the patient is controlled as well as possible by the internist once the diagnosis has been established. The general consensus is that the complication of retinopathy is less frequent and less severe in the well-controlled diabetic. Colwell (*59*) has recently noted that the second stage of retinopathy (punctate hemorrhages, exudates) is the stage most affected by good control.

The various factors incriminated in the past are regulated where possible. These include:

1. Serum mucopolysaccharides and lipids and lipoproteins. These are elevated frequently but are believed to be nonspecific changes.
2. Adrenal cortical hormones. There is considerable data (*10*) implicating the adrenal cortex in retinopathy. A reduction in adrenal cortical function seems to have a favorable effect on diabetic retinopathy. However, there is also evidence that there is no adrenal cortical hyperfunction in patients with uncomplicated diabetes, diabetic retinopathy, and nephropathy (Rifkin, Solomon, Lieberman 1958 (*60*). These discrepancies may be due to the fluctuations of steroids in the course of the disease.
3. Maintenance of normal intraocular pressure.
4. Maintenance of normal vascular tone.
5. Maintenance of normal intravascular properties; e.g., viscosity.
6. Anabolic steroids have been tried with some favorable influence (Houtsmüller et al. (*61*)).
7. Salicylates were introduced into the therapy of retinopathy because it has been noted that diabetic patients receiving salicylates for other reasons seemed to develop fewer vascular complications.
8. Among the disappointing therapies tried have been the use of anticapillary fragility factors, anticoagulants, lipotropic substances, low salt, low fat, high-unsaturated fat diets, massive vitamin B_{12} and B-complex administrations, and ocular X-ray irradiation (*5*).

Many of these factors are interdependent, and usually therapeutic approaches have not been well controlled. Some well-controlled studies have been discouraging, such as the use of testosterone (Bedrossian 1953 (*62*)), but others have been encouraging.

RELATION OF CONTROL OF DIABETES TO DIABETIC RETINOPATHY

Role of Heredity

It is generally accepted that the tendency to diabetes mellitus is inherited. However, there is disagreement as to whether the diabetic inherits a single trait, that of the metabolic defect which, if uncorrected, favors vascular disease, or whether he inherits two separate and basically independent traits—one trait determining the metabolic defect, and the other directing the vascular course. Both run concurrently but may have independent courses. It is also possible that both the metabolic deficit and the vascular disease may stem from a cominon inherited abnormality of unknown nature.

There is some evidence for insulin deficiency being a primary factor in the development of retinopathy. The production of experimental diabetic retinopathy in dogs by the use of alloxan and growth hormones by Hausler et al. (*54*), Engermann and Bloodworth (*55*) would favor the currently accepted hereditary etiology of this vascular complication (*4*). Removal or damage of the pancreas in humans has been followed by retinopathy and nephropathy (Duncan et al. 1958 (*63*); Lawrence 1949 (*64*); Sprague 1962 (*65*)). There is some controversy concerning hemachromatosis (Becker and Mills 1960 (*66*); Lonergan and Robbins 1959 (*67*)). However, the evidence is sufficient to make it difficult to disregard the possibility that diabetic microangiopathy may be due to lack of insulin. A hereditary factor could still be the one that selects those who will suffer this particular consequence of insulin deficiency.

Studies With Control

For conclusive results, prospective studies must be done. Patients should be observed from the onset of discovery of diabetes. Well-treated patients should be matched with poorly controlled ones. They

should be similar in age, sex, duration of diabetes, age of onset of diabetes, and so on.

Such studies might be considered impractical and unjustifiable, particularly on those who become diabetic before 30 and thus are prone to ketosis and dependent on insulin. For this reason, retrospective studies have received and probably will continue to receive the most attention.

From a review of presently available studies, Marble (*68*) has concluded that degree of control is a definite factor. However, the factor of ease of control has not been eliminated. The patients in one group may, for some unidentified reason, be brought under reasonable control with greater ease than those in another group. Is it the nature of their disease that allows them to respond to diet, sulfonylureas, biguanides, and insulin? Why do some patients with good control develop vascular disease and some with obviously poor control stay free of such complications?

Why are retinopathy and nephropathy sometimes present at the moment of discovery of the diabetes? Sometimes these conditions may appear in patients before there is evidence of chemical diabetes, that is, cases of so-called prediabetes.

If insulin contributes to these complications, how?

Is insulin the factor that leads to basement membrane thickening?

Does the inadequacy of insulin lead to other pathways for glucose utilization, with deposition in the basement membrane?

Influence of Hypophysectomy

Following Poulsen's demonstration of amelioration of diabetic retinopathy in a young woman who suffered postpartum necrosis of the pituitary, hypophysectomies have been performed in a limited number of patients at the varying stages of advanced retinopathy.

In the past decade, the pituitary function has been reduced by hypophysectomy, hypophyseal stalk section, cryosurgery, implantation of yttrium in the pituitary fossa, and by other forms of irradiation; e.g., proton (*13*) and betatron. The results have not been consistent. Ophthalmologists anxious to help their suffering diabetic patients are confused by the varying reports, the lack of controls, and the absence of a reasonable baseline to allow proper evaluation of this drastic technique (*69, 70*).

In a recent symposium reporting on diabetes, 11 groups actively engaged in a study of the effects of induced hypopituitarism and hypoadrenalism discussed their results. Almost all agreed that, in most patients, there was a dramatic reduction in the need for insulin and a clearing of vitreous and retinal hemorrhages. Serious operative complications were seen. Death, the need for exogenous cortisone, hypoglycemia, and hypotension were encountered. The renal complications, neuropathy, and life expectancy were not improved. To date, 387 patients have been treated in this fashion, of whom 8.8 percent have died as a result of the initial surgery. The visual status has been improved or stabilized in approximately 50 percent.

There has been, in the favorable cases, a reduced tendency to preretinal and vitreous hemorrhage, cessation of neovascularization, reduction in venular dilatation, and obliteration of new vessels. Little or no change has been noted in fibrous sheaths of advanced proliferans.

The data do not clarify whether total or partial ablation of the pituitary is better, or whether the results merit operation on diabetic patients prior to the existence of retinopathy.

It is apparent that further well-controlled studies on the pituitary role in diabetic retinopathy and the influence of anabolic steroids on this disease are mandatory.

Prediabetes

Studies have shown a variety of changes in prediabetics when compared with findings in normal control subjects without a family history of diabetes. "Prediabetics" may be defined as persons most likely to develop the disease. These are individuals both of whose parents or whose identical twins have diabetes. The term also applies to those with close relatives with diabetes, women with an abnormal obstetrical history, obese individuals, and subjects with diabeticlike vascular manifestations.

The characteristic changes include vascular lesions in the ear lobe, and in the subpapillary dermal plexus, gingival tissue, bulbar conjunctiva, finger pulse wave, and renal biopsies.

These changes could be related to some decrease in the metabolic effectiveness of insulin. Perhaps it is due to modification in the chemical structure of the insulin, to an altered insulin, or to an inhibiting factor in the blood or at the tissue level.

Perhaps therapy could keep such patients from advancing to frank, clinically recognizable diabetes and to progressive vascular lesions.

The roles of stress, infections, and endocrinopathy must be evaluated. Therapy against these and obesity might play a preventive role. Would the use of sulfonylureas or biguanides stop the progression at this stage?

The ophthalmolgist, in the meantime, provides optical aids where helpful, notes the course of the disease, and operates where retinal detachments of diabetic origin might respond and otherwise intractable hemorrhage glaucoma might demand.

SUMMARY

Diabetes mellitus affects the ocular structures in many ways. Fortunately, many of these changes are not vision threatening; but the involvement of the retinal vessels, and secondarily of the vitreous, is a major cause of visual loss. This diabetic manifestation is usually a late one and therefore should be preventable; but to date, no successful measures have been demonstrated. Once the vascular lesions occur, further progression occurs at varying rates. Modern therapy may alter the rate of progression in a fortunate minority. Not all researchers are convinced that this slowing down is really physician induced, however. This disease process begs for and merits research support until conquered. The need is evident from the economic and social as well as the scientific aspects. In Massachusetts and New York State in 1962, 18 and 19 percent, respectively, of newly reported cases of blindness (as legally defined) were due to diabetes (New York State Commission for the Blind annual report, 1962; Massachusetts Department of Public Health, Division of the Blind annual report, 1962).

There are many areas where future studies could be be helpful in solving or leading to the solution of this pressing problem.

Biochemistry

1. *Insulin transport and action*
   a. Abnormal production or secretion
   b. Abnormal form
   c. Defect in peripheral tissue response
   d. Inhibition of insulin activity by antagonists
   e. Penetration of insulin to tissue site
2. *Basement membrane*
   a. Chemical nature of deposit—normal and abnormal
   b. Mechanism leading to thickened membrane—defect in production or breakdown

Physiology

1. *Factors responsible for dynamic state of diabetes*
   a. The ebb and flow of blood-sugar levels
   b. The reason for remissions
2. *Prediabetes*
   a. Improved methods of recognition
   b. Factors which hasten or deter path to overt clinical diabetes
3. *Insulin resistance—nature*
   a. Chemical
   b. Immunogenic
   c. Hormonal
   d. Relationship to microangiopathy
4. *Other factors influencing insulin activity at the local tissue level*
   a. Penetration
5. *Experimental production of microangiopathy*
   a. Pancreatectomy alone
   b. Pancreatectomy plus growth hormone
   c. Alloxan alone
   d. Alloxan plus growth hormone
   e. Influence of species studied
   f. Spontaneous diabetes and retinopathy in experimental animals
   g. Role of immunogenic mechanisms
   h. Retinopathy and nephropathy—variations in production

Genetics

1. *Genetic patterns for diabetes and for microangiopathy*
   a. Possible genetic-pattern influence on
      1. Vascular changes
      2. Response to normal and abnormal insulin
      3. Response to sulfonylureas
      4. Response to autonomic agents
      5. Response to hormones
   b. Role of genetics in prognosis
      1. Remission
      2. Pancreatic resistance

Therapy

1. *Value of early detections*
   a. Prolongation of life?
   b. Avoidance of complications?
2. *Control*
   a. Definition—needs clarification
   b. Prospective *vs.* retrospective studies
3. *Prediabetes*
   a. Value of therapy against stress, endocrinologic factors, use of sulfonylureas
4. *Hypophysectomy and hypothalamic interference*
   a. Surgical interference
   b. Irradiation
   c. Chemical suppression
   d. Anabolic steroids
   e. Necessity of prospective studies—controls
   f. Role of growth hormone and other pituitary secretions
5. *Psychological aspects—influence on course of disease*
   a. Initial phase before diagnosis established
   b. Phase when diagnosis established
   c. Phase when chronic course demands close surveillance
   d. Phase when complications become known to patient and realization that rigid therapy may fail
   e. Phase when visual failure is imminent

Histopathology

1. Descriptive histopathology by light and electron microscopy would appear to offer little by itself.

2. The available techniques are important in delineating experimentally induced microangiopathy and in studying new approaches to the basement membrane, permeability of capillaries, and influence of pharmacologic agents.

Epidemiology

1. Incidence.
2. Prognosis.

There can be no doubt that research support in this area is mandatory. There are many unexplored avenues that may lead to exciting new pathways and, eventually, to a solution.

Symposia have been helpful in correlating, clarifying, and stimulating research. However, too many symposia defeat their own purpose. The participants are occupied with preparation, presentation, and publication. They might utilize the time and the funds to greater advantage in investigation. Symposia do occasionally introduce a new discipline into ophthalmology. Usually most of the participants are already aware of the accomplishments and possibilities in the field. Certainly they are after a few published symposia on the subject are available.

Support of the research leads suggested can be rewarding. However, at no time should the topic be chosen in preference to the individual researcher. It is tempting and easier to support programs set up by planners, than to invest in the original thinking of outstanding individuals; but in all fields, we must have new ideas and creative people. These—not institutions, and not places—should get priority in allocation of funds.

This document demonstrates the need for continued and increased support for this field. Such support is justified economically and socially as well as scientifically.

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Chapter 15—CONGENITAL AND DEVELOPMENTAL MALFORMATIONS OF THE EYE

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INTRODUCTION

A very important category of serious eye diseases typically associated with severe bilateral visual disability is that of abnormal growth and development of the eye before birth (congenital malformations) and/or during the first few years after birth (developmental disorders). Much has been learned about some of the causes of these ocular malformations, and in certain cases, this information makes prevention possible. In addition to abnormal genes and chromosomes, responsible factors include infectious agents (bacteria, viruses, and protozoa), inadequate diet (maternal and neonatal), and untoward reactions to drugs and other therapeutic agents. This category is especially important for socioeconomic reasons. The ocular lesions are frequently bilateral and totally disabling. When the patient is otherwise healthy he may be faced with a long but totally blind life. The economic aspects of blinding diseases of the newborn are considered in part I of this report. report.

INFECTIOUS CAUSES

Transplacental infection from a syphilitic mother has long been widely recognized as an important cause of blindness, as has gonorrheal infection acquired by the baby during birth. Once very prevalent diseases, both of these have been virtually eliminated in modern, civilized countries by appropriate therapeutic and preventive measures. More recently, the importance of transplacental infection as a cause of serious eye disease has become widely recognized in toxoplasmosis, cytomegalic virus infection, and German measles (*1*).

The fact that maternal German measles (rubella) in the first 2 months of pregnancy is often associated with cataracts and other ocular lesions in the newborn baby has been a generally appreciated but unexplained fact for 25 years. Since the causative virus of German measles had not been isolated and because this disease was not reproducible in experimental animals, there was no way of determining how this mild, transient, sometimes completely subclinical disease in the mother could produce such permanent, disabling malformations in the infant. Recently, however, with the development of technical methods for recovery of the virus from nasal secretions, urine, feces, and various tissues, it has become well established that the "rubella baby" is actually still infected at the time of birth. Moreover, the virus has been recovered from the cataractous lens and from the aqueous humor. This affords a very satisfactory explanation for the heretofore mysterious observation that the rubella cataract is not always bilateral: if the virus manages to invade and establish itself in the rapidly proliferating epithelium of only one lens, the other lens will develop normally.

Several preventive measures are now possible. "Rubella parties" for little girls and artificial immunization may prevent maternal rubella later on, and therapeutic abortion can prevent the birth of a malformed baby. Recognition of the fact that rubella babies may continue to excrete the virus for a year or more after birth indicates the need for use of appropriate isolation techniques when these patients are seen in a physician's office or in the hospital. The prevention of congenital toxoplasmosis and cytomegalic disease is not possible because the source of these infections and their mode of transmission to the mother are unknown.

DIETARY CAUSES

The most important dietary cause of serious ocular disease is avitaminosis A. There are still several underdeveloped countries in the world where the dietary inadequacy in vitamin A and the lack of funds to provide supplemental vitamins have permitted the preventable disease, keratomalacia, to remain widespread (*2*). This condition leads to destruction of the cornea, with perforation, infection, disorganization of the eye, and permanent blindness. In less severe cases, the permanent damage may be limited to corneal scarring, correctable by corneal transplantation.

METABOLIC DISORDERS

Another cause of blindness that is preventable by dietary measures is galactosemia. In this condition, the baby is born with an enzymic defect that renders him incapable of properly metabolizing the galactose in milk. Malnutrition, enlargement of the liver, cataracts, and galactosemia are the main clinical features. Elevated levels of galactose in the aqueous humor trigger the enzyme aldose reductase to convert galactose to dulcitol. The accumulation of this sugar alcohol in the lens will lead to irreversible cataract formation if the condition is not recognized early in the neonatal period and a galactose-free diet instituted (*3*). A number of other metabolic diseases have also been found to have serious ocular complications (for example, juvenile diabetes, ochronosis, cystinosis, homocystinuria, and Lowe's syndrome); and with the rapid advances that are being made in biochemistry, genetics, and the study of metabolic disorders, many additional entities will be recognized. Hopefully, some of them will be preventable or correctable.

IATROGENIC DISEASES

Some ocular malformations and developmental lesions of the newborn are iatrogenic—that is, complications of new medications or of more modern therapeutic methods. The thalidomide story is the most notorious recent example of the potential danger to the fetus of drugs ingested by a pregnant woman. A high incidence of ocular abnormalities, including some very serious malformations, has been observed among thalidomide babies (*1*).

Another very important iatrogenic disease of the newborn baby is retrolental fibroplasia, the retinopathy that is induced by administering high concentrations of oxygen to premature infants. This disease made its appearance rather explosively in countries that had the most modern, well-equipped nurseries and provided the best medical care for the premature baby. Astute epidemiologic observations and ingenious experimental work by clinical ophthalmologists and ophthalmic pathologists led to the conclusion that the capillaries of the premature baby's retina are intensely sensitive to hyperoxygenation. With appropriate changes in the use of oxygen for management of premature babies, the incidence of this disease fell as dramatically as the disease had appeared (*4*). The significance of retrolental fibroplasia as a cause of blindness in children is considered in greater detail elsewhere in this report.

GENETICALLY DETERMINED

The occurrence of genetically determined ocular disease is, of course, well recognized, and several recently published volumes attest to the worldwide interest in this subject. This group of disorders varies tremendously in scope, ranging from less serious conditions, such as color blindness, to very disabling diseases, such as retinitis pigmentosa. The examples just cited are essentially diseases of the eye, but in many hereditary diseases, the ocular tissues are merely one among many that are affected (for example, von Recklinghausen's neurofibromatosis, and the other phacomatoses; gargoylism, and the related mucopolysaccharidoses; arachnodactyly; and so on). In some of these genetically determined diseases, ocular lesions occur only occasionally (e.g., the retinal harmartomas of tuberous sclerosis), while in others they occur so regularly that they are very important in clinical diagnosis (e.g., the Kayser-Fleischer ring of Wilson's disease). Some of these ocular manifestations are of no great functional significance, but others (e.g., the corneal lesions of the mucopolysaccharidoses) may be disabling.

While the ophthalmologist has nothing to offer therapeutically in some of these disorders, there are other cases (e.g., the corneal dystrophies and certain familial cataracts) in which surgical removal of the diseased tissues can restore vision. There are also conditions in which surgical and medical therapy may help control a difficult situation (e.g., the glaucomas associated with certain hereditary disorders; retinoschisis and retinal detachment; bleeding from retinal vascular malformations; etc.).

Thus the ocular manifestations of hereditary diseases are important for several different reasons: In diagnosis and differential diagnosis, because of their functional significance, and for therapeutic considerations.

Most important, however, is the need for thorough familiarity with the genetically determined diseases, so that the physician can not only make correct clinical diagnoses and institute appropriate therapy, but also detect other affected members of the family, including carriers of abnormal genes, and render service in genetic counseling.

CHROMOSOMAL ABERRATIONS

During the past 5 years, another group of congenital malformations characterized by recognizable chromosomal aberrations has been discovered. The aberration may be an extra chromosome, a missing chromosome, or a defective chromosome (*5*). These chromosomal abnormalities are detected by cytologic studies of the patient's cells, grown in tissue culture (*6*). Such studies, therefore, can only be made on living patients, and they are not applicable in the retrospective analysis of autopsy cases. Since some of the diseases attributable to the presence of an extra chromosome (e.g., the retinal dysplasia syndrome due to an extra chromosome in the 13 to 15

or D group) are characterized by lethal cardiovascular and/or cerebral malformations, the malformed babies are often stillborn or die early in the neonatal period. Thus it is not surprising that relatively few cases have been investigated for the presence of abnormal chromosomes. Still, ocular lesions are so distinctive that, together with other characteristic visceral anomalies, they permit the pathologist to differentiate anatomically the 13 to 15 trisomy from other ocular malformations (*1*). The etiology of these chromosomal disorders is unknown.

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Chapter 16—RETROLENTAL FIBROPLASIA: RECENT CONTRIBUTIONS AND RESEARCH APPROACHES

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INTRODUCTION

Retrolental fibroplasia, one of the more formidable iatrogenic conditions of this century, has in the majority of cases been unknowingly induced in the name of good medicine. The disorder occurs most frequently in premature infants who have been exposed to oxygen in concentrations over that found under normal atmospheric conditions (20 percent). The pathogenesis of the disease has been divided into two phases: An initial constriction of the retinal vessels, followed by a dilatation of the vessels with an exuberant overgrowth of capillaries in a disorganized fashion. In the latter phase, retinal and vitreous hemorrhages occur, new vessels grow into the vitreous, and a fibrotic reaction takes place; this, by traction on the retina, may eventually detach the retina, producing the retrolental mass. When the process reaches this final stage, the infant will be left functionally blind.

The elucidation of the factors which contributed to the induction and progression of this condition represents a significant medical achievement. It should be understood that many questions remain unanswered. The solution of these problems has become even more urgent recently because of the increased therapeutic use of oxygen under hyperbaric conditions.

PAST CLINICAL CONTRIBUTIONS

Retrolental fibroplasia (RLF) was first described, named, and associated with prematurity by Terry in 1942 (*1*). Although cases closely resembling RLF had been published previously (see Ryan (*2*)), the timely reports of Terry (*1, 3–6*) and the increasing incidence of the process (*7–9*) brought about its widespread recognition. A multiplicity of theories, etiologic agents, and treatments were considered and partially evaluated by 1962 (*10*). There was general acceptance that the incidence of the disease was significantly greater in the premature than in the full-term infant. The effect of oxygen was thought to be one of the more important possible causes needing further evaluation (*10*).

Ingalls (*11*) and Szewczyk (*12*) held the viewpoint that anoxia, either during gestation or in the early postnatal period, was responsible. Szewczyk (*12*) reported that too rapid weaning of infants from oxygen-rich environments induced the process and that placing children in whom the disease had already manifested itself back into oxygen was beneficial. This opinion continues to have its proponents (*13*). By subjecting pregnant mice to anoxic conditions (low-atmospheric pressures) for a specific time during gestation (16 ± 1.5 days), Ingalls (*14*) induced ocular lesions that in part resembled RFL.

At the same time, it became clinically evident that infants placed under high-oxygen tensions showed an increased incidence of the disease (*2, 15–18*). On this basis, oxygen administration was curtailed in hospitals where the disease had been prevalent, with the result that a case was encountered only rarely (*2, 15, 16, 18*). Patz et al. (*17*) first subjected the oxygen-toxicity theory to a controlled study. Alternate infants with a birth weight under 3.5 pounds were placed either into a 65- to 70-percent oxygen environment for 4 to 7 weeks, with gradual weaning to air, or into oxygen below 40 percent from 25 hours to 2 weeks, with rapid weaning. In the high-oxygen-tension group, 61 percent of the infants developed RLF, while only 16 percent of the low-oxygen group had any manifestations of the disease. No severe cases came from the latter group.

These experiments culminated in a cooperative controlled study on 586 infants weighing 1,500 grams or less at birth (*19*). Again, a much higher incidence was found in a high-oxygen-tension group. The mortality rate was the same in infants kept in over 50 percent oxygen continuously for 28 days and those given oxygen only when deemed necessary. The risk of developing the disease was found to be greater among infants born of a multiparous pregnancy. *It was concluded that there was "no concen-*

tration of oxygen in excess of that found in air that is not associated with risk of developing RLF."

RECENT CLINICAL CONTRIBUTIONS

The oxygen-toxicity theory was generally accepted, and the recommendations of the cooperative study followed. Many recent contributions in this field deal with the reduced incidence of RLF (*20–23*). Cases are still being reported for which no or low-oxygen therapy has been utilized (*21–26*), suggesting that factors other than oxygen must be incriminated in these infants (*25*). *In agreement with the cooperative study's suggestion of avoidance of all unnecessary oxygen therapy (19), it was reported (27) that, whereas the newborn's arterial oxygen tensions is 86 mm. Hg. (28), a mildly cyanotic child placed in a 40-percent oxygen environment may increase his arterial oxygen tension to 240 mm. Hg.* Such an infant may also have a patent ductus arteriosus with a right to left shunt, causing the oxygen concentration delivered to the head and eyes to be higher than that delivered to the rest of the body. Experimental evidence for the ductus remaining patent during neonatal anoxia has recently been demonstrated in the dog (*29*).

The long-term effects of RLF on the eye (*22, 30*), central nervous system (*31–34*), and general development (*32*) have been the subject of many recent reports. In a followup study of children who developed RLF from 1949 to 1953, it was found that most of the blind children came from the group that had at some time gone through the stage of forming a partial or complete retrolental membrane (*22*). Only a small number of children were blind from a lesser degree of involvement, including those who had been observed during the course of their disease to have had vitreous strands, retinal folds, peripheral membranes, and a "dragged" disc. The percentage of children having degrees of visual loss less than blindness was about equal for each grade of RLF below the most severe involvement. This led the authors to believe that another factor might be involved. The amount of myopia and myopic astigmatism increased with the severity of the RLF. The incidence of heterotropia was proportional to the severity of RLF, increasing significantly with the most severe grade. RLF must be considered in the differential diagnosis in young children with spontaneous hyphemas (*35*), iritis of infancy (*36*), retinoschisis (*37*), heterotopic maculae (*30*), pseudoextropia (*38, 39*) (even with fusional ability (*30*)), pseudoglioma, and leukokoria (*40*).

Females from the Boston Lying-in Hospital RLF group were used in a study showing that, in contrast to animals, blindness from an early age in the human leads to an earlier onset of the menarchy, whether or not prematurity is present (*41*).

The relationship of mental retardation to RLF is difficult to estimate because of the many variables involved. Factors such as: (1) The degree to which blindness affects the results of various psychological tests, the general acquisition of knowledge, and the child's overall psychiatric problems; (2) the effect of prematurity itself on learning ability; (3) the reasons for prematurity; and (4) the medical condition of the child during the neonatal period must be considered. It was originally believed that many RLF children had cerebral damage (*8*), and recent reports tend to support this concept (*31–34*). In one study, mental retardation was found in 32 percent of the children blind from RLF and in 41 percent of those blind from other causes (*31*). Unfortunately, two-thirds of those blind from other causes had optic atrophy, which might be evidence of more generalized cerebral damage. In a study matching children for birth weight, sex, and race, IQ tests at the age of 7½ years demonstrated a rating of 92.3 for RLF premature children and 101.0 for matched controls without RLF (*33*). Since only 10 of the 58 children with RLF were considered visually handicapped, the results excluding the 10 visually handicapped children from the data would have been of interest. Bender and Andermann (*34*) considered the cerebral damage found in RLF to be due to intrauterine disorders and prematurity rather than to the high oxygen itself. McDonald claimed an inverse relationship between the incidence of RLF and cerebral palsy (*42*). Curtailment of the use of oxygen was believed responsible for this higher incidence of cerebral palsy. Abnormal electroencephalograms were frequently encountered in children with severe RLF (*32*). The incidence of systemic involvement other than in the eye and the brain is difficult to evaluate because of the lack of a controlled series in the literature.

SOCIAL ASPECTS

The introduction of an estimated several thousand visually handicapped RLF children into society created problems of significant magnitude. The daily hardships imposed on the individual child and his parents are inestimable. As school age was reached, facilities in schools for the blind had to be expanded and new schools built. More teachers were employed and trained in special methods of education. These requirements were successfully met.

Presently, the majority of these children are in high school or starting a vocation. Very little information is available in the medical literature concerning the present status of this group. A number of problems exist which should be reviewed for the

future proper management and financial support of these individuals. The most urgent questions at the present time (as briefly outlined below) pertain to their future education and employment.

1. What percentage of children complete all grades for which educational facilities exist?

What were the reasons they left school prior to completion?

What is the present status of these dropouts as to their employment and psychologic attitudes?

What opportunities are open to these children for either further education or employment?

2. What type of vocational counseling and training is available?

What use is being made of these opportunities?

What percentage of individuals are gainfully employed after such training?

3. How many of these children are capable of a college education?

What are the opportunities for higher education?

Is advantage being taken of the opportunities presently available?

It is only through this type of survey that sufficient information can be obtained to satisfactorily help these children develop their fullest potential and become as self-sufficient as possible.

EXPERIMENTAL STUDIES

Concomitantly with the first clinical impression of the toxicity of oxygen, the problem was brought into the laboratory. High-oxygen environments were found capable of inducing a condition which, in part, closely resembled human RLF in the eyes of newborn mice (*43, 44*), ratlings, (*44*), kittens (*45*), and puppies (*44*). On direct observation of newborn kittens' retinal blood vessels, high-oxygen tensions were seen to induce vasoconstriction and capillary obliteration in 5 minutes (*46*). This state lasted for 5 minutes and was followed by vasodilatation. After 6 hours of exposure, a gradual total vaso-obliteration recommenced and was completed in 8 hours. In injected specimens, this total obliteration actually was not completed for 36 hours (*47*). It began in the advancing periphery of vascular ingrowth in the immature retina of the kitten (*47*) but at the posterior pole of the ratling (*48*). The earliest changes in the human occur in the equatorial zone (*49, 50*). Although the obliterative phase was not frequently recognized clinically, it was observed when looked for specifically (*17*). Oxygen concentrations below 40 percent were not effective in obliterating the retinal vessels (*47, 51, 52*).

Retinal detachments allowed the obliterated vessels to dilate again; but, unlike the pattern in humans, these detachments were not progressive. Instead, they halted the pathologic process (*53*). Sympathectomy (*51, 54*) and carbon dioxide (*47, 51*) had no influence on the obliterative phase. This effect of oxygen, carbon dioxide, and sympathectomy on the immature retinal vessels resembles the effects seen on the patent ductus arteriosus, in which the relatively high-arterial oxygen pressure of extrauterine life is thought to initiate closure (*55–57*). Vascular proliferation occurred under prolonged exposure to oxygen (*58, 59*) but was retarded in comparison with the neovascularization that took place after removal from high-oxygen tensions.

On the electron microscopic level, the first changes which occurred in the kitten's immature vascular system after exposure to 6 hours of 70 to 80 percent of oxygen was a cytoplasmic degeneration in endothelial polyps protruding into the capillary lumen (*60*). With more prolonged exposure to oxygen, general cytoplasmic disruption and pyknosis developed. Little swelling was noted in adjacent retinal tissue, refuting the author's former belief that retinal swelling was the primary cause of the vaso-obliteration (*61*). The degenerating cells migrated or were displaced to less affected areas, forming islands of cells between capillary skeletons. Gradually these islands disintegrated. This process has been termed "retraction" and appears to be an acceleration of a normal physiologic phenomenon (*60*). The capillaries stained with periodic-acid Schiff stain (*58*); in immature vessels not exposed to high-oxygen concentrations, no staining was observed. A finding similar to this occurs in lungs subjected to abnormal oxygen tensions (*62*).

The toxicity of one atmosphere oxygen and above on certain sulfhydryl-independent respiratory enzymes has been well documented (*63–65*). Hellström could demonstrate no difference in retinal succinic dehydrogenase activity in comparing retinas removed from newborn mice kept under high-oxygen concentration with those of the controls (*66*). The retinal oxygen tension never reached the levels used in experiments in vitro.

On the animals being brought back to air, intense angioblastic activity took place, with vascular proliferation into the retina and the vitreous (*44, 47, 67*). Ashton and Black (*48*) held that this phase of the disease took place only when oxygen tensions were reduced; Hellström (*59*) and Patz (*58*) thought that it could occur in continuously oxygen-rich environments. No difference in proliferative activity could be found between those animals weaned and those brought abruptly out of high-oxygen concentrations (*68*). Venous stasis was considered an important factor in all types of retinal neovascularization, including RLF (*69*).

Hypothermia was protective against oxygen toxicity on the immature retina (*70*). Recently, hypothermia has been shown to decrease the mortality rate of mice breathing 99 percent oxygen (*71*). It likewise has been shown to protect the succinic dehydrogenase system against high-oxygen pressures in vitro (*63*).

The degree of retinal vascular maturity has a decided influence on the production of RLF. Attempts in the past to produce RLF in the embryo mouse (*44*), rat (*44*), and kitten (*68*) by exposure of the mother to oxygen during gestation were unsuccessful. Fujikura (*72*) recently produced RLF in newborn rabbits by exposing the pregnant mother to hyperbaric oxygen (97 to 100 percent oxygen cycling 1 to 3 pounds per square inch above ambient pressures for 15 hours). No maternal arterial or venous oxygen tensions were taken. This experiment must be interpreted in the light of the severe pulmonary damage caused by prolonged high-oxygen breathing (*62*). The author stated that no apparent respiratory distress was present in the mothers. However, an anoxic preparation cannot be excluded (see Ingalls et al. (*14*)). In the mouse, the retina does not become fully vascularized until 10 days of age (*73*). With increasing vascularization, the vascular changes became more difficult to induce and those which did occur took place progressively in the more peripheral retina. RLF-like pathology could not be induced in the fully vascularized newborn or in the adult retina (*58*). The human retina is not fully vascularized until the eighth month (approximately 1,700 grams) of fetal life (*58*). The effects of oxygen on the mature vascular system will be discussed in the section on hyperbaric oxygenation.

In summarizing these data, it can be said that an initial vasoconstrictive phase occurs, probably induced by the high-tissue oxygen tension. A relative anoxia of the retina is subsequently produced. Anoxia is considered to be a growth stimulus to immature vessels and the reason why arteries have a capillary-free zone which veins lack (*74*). The vascular proliferation may be kept in check under continued high-oxygen tensions by a relatively high-retinal oxygen tension supplied via the choroidal circulation (*58*). Whenever the inspired concentrated oxygen is reduced, the retinal oxygen tension is lowered, because the choroid no longer is an enriched source, and many of the retinal capillaries are permanently obliterated. Vascular growth recommences in a disorderly fashion because preexisting channels for vascularization no longer exist (*58*). Concomitant venous stasis may be an important factor in this neovascularization (*69*).

UNANSWERED PROBLEMS

Many questions concerning RLF remain to be answered. Why do certain full-term children develop RLF without being subjected to increased oxygen tensions? Full-term infants' retinas may show variability as to the extent of their retinal vascularization. If the age of completion of retinal vascularization were considered to fit a Gaussian distribution curve, these full-term infants might be at the extreme right end of the curve. The only experimental evidence of this variability in growth is that of Patz (*75*).

The other side of this problem is that certain premature infants under high-oxygen environments do not develop RLF. These infants could be at the other end of the Gaussian distribution curve and have fully vascularized retinas at 5 or 6 months of fetal life. Another possibility is that they may not be as well oxygenated as expected. The fact that sick children developed less RLF than well children did could be confirmatory evidence (*19*). However, it is not known how many of the sick infants were cyanotic or had respiratory difficulties. It would be surprising to find RLF in a child with a right to left intracardiac shunt. Evidence for this lack of high-arterial oxygen pressure under high-oxygen concentration could be assessed only by taking direct arterial oxygen tensions.

It has been shown that carbon dioxide does not counteract the gross vasoconstrictive effects of oxygen on retinal immature vessels (*47, 51*). This is in contrast to its marked effect on cerebral vessels (*76, 77*). The more subtle actions of carbon dioxide on the retina and the retinal blood vessels are unknown. With higher oxygen concentrations, more oxygen is carried to the plasma and less fetal hemoglobin has to be reduced for the same tissue requirements. Oxyhemoglobin is much less capable than reduced hemoglobin of forming carbaminohemoglobin, an important carbon dioxide transport system. Hypercapnia would develop at the venous end of the capillary. The resulting acidosis could lead to considerable intracellular electrolyte disturbance. Such problems are much more serious under hyperbaric oxygenation. The only method of evaluating the importance of this effect would be to measure venous carbon dioxide pressures and blood pH. Estimation of the protective action of such agents as THAM [Tris (hydroxymethy) aminoethane] would help evaluate this hypothesis (*78*).

The newborn's metabolic rate may be significant (*79*). Whereas hypothermia has a protective action (*70*), the effects of hyperthermia or thyroid administration may have an adverse effect.

Mural cell participation in RLF is not at all understood. Ashton (*60*), Kuwabara, and Cogan (*80*) consider mural cells uncommon on proliferating capil-

laries. Mutlu and Leopold (*81*) found them present on newly forming vessels. Kuwabara and Cogan (*80*) thought that pericytes would be washed away by trypsin digestion because of the lack of basement membrane encasement. Thus, it would not be surprising to find few mural cells in a trypsin-digested preparation of immature capillaries, which have no apparent basement membrane (*60, 82*). Mutlu and Leopold (*81*), on the other hand, used both distilled water and trypsin-digestion techniques, but they did not state whether these techniques made a difference in the preservation of the mural cells. If such cells do exist on these capillaries, their role in experimentally induced RLF would certainly call for investigative study. It is of interest to note that the capillaries with few or no mural cells, such as diabetic neovessels and corneal vessels (*68, 82*), are incapable of being obliterated by oxygen (*83*), even under hyperbaric oxygenation (*84, 85*). It may also be true that capillaries without a basement membrane are capable of oxygen obliteration, while those with basement membranes (diabetic new vessels (*82*)) are incapable of this. Contrary to this hypothesis is the finding that the earliest cell damage occurs near the lumenal side of the endothelial cell; i..e., the side which never develops a basement membrane (*60*).

The effects of oxygen on enzymes of the Krebs cycle should not be discounted despite the negative report of Hellström on succinic dehydrogenase activity (*66*). Kuwabara and Cogan (*80*) found only slight succinic dehydrogenase activity in both mural and endothelial cells in adult retinas. Their techniques should be used to study this system under high-oxygen pressures along with attempts to protect the enzyme. Manganese sulfate has recently been shown to protect rats from convulsions induced by hyperbaric oxygen (*86*). Succinic dehydrogenase is likewise protected by manganese from the effects of excessive oxygen (*64*). What hyperoxia does to the changing metabolic system of the newborn eye is unknown (*87*).

As noted before, retinal detachment reverses the vaso-obliterative stage (*53*). The pathophysiology of a system in which the vaso-obliterative stage could be continued by means other than oxygen under detachment conditions should shed further light on the theory claiming anoxia as a vascular growth stimulus. The possibility exists that the vaso-obliterative phase is more dependent on oxygen supplied via the choridal circulation than has been previously assumed.

No investigations of the effect of oxygen on the lysozomes ot the retinal vasculature have been carried out. Recently, it has been shown that lysozomes are labilized by oxygen (*88, 89*). Such a mechanism (*90, 91*) could account for the electron microscopic findings (*60*). Against this hypothesis is the generally poor result achieved with ACTH therapy (*92, 93*), although therapy may have been started too late to be truly beneficial in most cases. Steroids have a stabilizing effect on lysozomes.

HYPERBARIC OXYGENATION

RLF has become an uncommon condition. However, oxygen under nonphysiologic conditions is being used more frequently. These include hyperbaric oxygenation and hypobaric oxygenation in space travel. In its latter application, the retinal circulation appears to be unaffected (*94, 95, 96*).

Hyperbaric oxygenation is being used in the treatment of neonatal asphyxia (maximum time under oxygen, 38 minutes) (*97*), traumatic and hemorrhagic shock (*98*), carbon monoxide poisoning (*99*), anaerobic infections (*100*), and arterial insufficiency (*101*). It is utilized in conjunction with tumor irradiation (*102*) and cardiovascular surgery (*103*).

Ophthalmologically, hyperbaric oxygenation has shown a number of interesting effects. It has long been known that oxygen in high concentration under ambient pressures produces a vasoconstrictive effect on the normal individual's retinal arteries and veins (*104–106*). In the normal subject, the retinal artery reactivity varies from 11.5 (*105*) to 24 percent (*104*). This decreased arterial caliber is associated with increase in the brightness of the venous blood (*104*). The role of CO_2 in reversing the constriction is controversial (*78, 105, 106*), but anoxia causes dilatation (*104*). The adult is said to lose 1 percent reactivity with every 10 years of life (*105*). Hypertensive patients have a reduced vascular reactivity (arterial reactivity equals 3.2 percent). Diabetics with hypertension have a lower reactivity (arterial reactivity equals 3.0 percent) than have diabetics without hypertension (arterial reactivity equals 4.2 percent) (*105*). The venous contractibility is also reduced (*105*). This decreased vascular reactivity correlates well with the same subject's loss of ability to react by increased cerebral flow to 5 percent CO_2 breathing (*107*). Under hyperbaric conditions (pressures of one to five atmospheres), with the subject breathing 100 percent oxygen, the greatest retinal vascular changes were found at two atmospheres. Small-artery constriction was greater than small-vein constriction, but large veins reacted to a greater extent than did large arteries (*108*). The resistance of diabetics to vasoconstriction has been demonstrated under hyperbaric conditions. Either no effect was noted (*85, 109*), or vasodilatation occurred (*109*).

Treatment of central retinal artery occlusion has not been successful (*109, 110*), but the lapse of time prior to the commencement of treatment may be an essential factor for success (*111*). As described previously, attempts at obliterating neovascularization

in the cornea by hyperoxia under ambient pressures (*69, 83*) and hyperbaric pressure (*84*) have been unsuccessful. No success has been achieved in obliterating diabetic retinal neovascularization (*85*). Central serous retinopathy has not responded to hyperbaric oxygenation (*109*). The effects of hyperbaric oxygen on the histology or biochemistry of the retinal capillary have not been investigated. In the newborn ratling, 100 percent oxygen at one atmosphere is capable of completely obliterating the capillaries (*112*). It is stated that this does not occur in the adult even under high-oxygen pressure (*69*), but it is not clear whether hyperbaric pressures were indicated.

When the central retinal artery is occluded by increasing intraocular pressure mechanically above the systolic ophthalmic artery pressure during hyperbaric oxygenation, visual perception is maintained for a much longer time than it is after occlusion under atmospheric conditions (*113, 114*).

Dogs subjected to a high-oxygen environment (680–760 mm. Hg.) for 75 continuous hours, or 85 hours interrupted by air breathing 1 to 2 hours per day, developed retinal detachments which subsided spontaneously (*115*). Lesser amounts of oxygen (610–680 mm. Hg.) did not induce detachments.

Exposure to high-oxygen concentration at ambient pressures and hyperbaric pressures caused changes in the electroretinogram and eventual retinal destruction in the adult rabbit (*116*). Irreversible changes were seen at concentrations as low as 60 percent at ambient pressures.

In man, breathing 100 percent oxygen under ambient pressures for 4 hours had no effect on the visual acuity or field (*117*). However, breathing oxygen under three atmospheres for 4 hours significantly reduced visual acuity, contracted the visual field, and produced pupillary dilatation (*118*). These changes occurred close to the maximum tolerated exposure and were reversible.

It is quite clear that high-oxygen concentrations at ambient pressures and hyperbaric pressures do have marked effects on the adult retina and retinal circulation. How hyperbaric oxygen affects the capillary endothelial cell, mural cell, and retina proper is not known. There must be a profound effect on the metabolism of the retina and its vasculature. Many of the hypotheses discussed under RLF become even more feasible as causes of oxygen poisoning under hyperbaric oxygenation. A great deal has been learned about RLF. Many of the techniques used in studying high-oxygen concentrations at ambient pressures could be used in examining the retinal circulation under hyperbaric oxygenation.

SUMMARY

A review of past and recent contributions to the field of RLF has shown that, although significant advances have been made, many problems regarding the relationship of oxygen to the pathogenesis of the disease remain to be solved. It has been clearly demonstrated clinically that the use of oxygen above that found under atmospheric conditions involves a risk of inducing RLF in the neonate.

In the past several years, oxygen has been administered with great frequency under hyperbaric conditions (increased pressure). This has already proven useful as therapy in a variety of medical conditions. Although ocular effects have been noted, these have appeared to be reversible in the mature eye and not comparable to the devastating effects of lower concentrations of oxygen on the premature infant. But insufficient work has been carried out along these lines to accurately determine the degree of oxygen toxicity on the retina. Hyperbaric oxygenation might also prove useful in the treatment of ophthalmic conditions despite the lack of evidence for this in the limited number of patients and conditions thus far studied. Knowledge accumulated in the past concerning RLF can be advantageously used in the field of hyperbaric oxygenation. Problems created by high-oxygen concentrations at ambient pressures are considerably magnified in hyperbaric oxygenation. Future clinical toxicity encountered in hyperoxia under hyperbaric pressures may be avoided by properly applied investigation.

RECOMMENDATIONS

It is recommended that the following projects be fully supported:

1. Experimental ocular embryology, especially projects designed to demonstrate biochemical and electron microscopic changes.
2. Further projects dealing with the effects of oxygen on the biochemistry, histology, electron microscopy, and flat preparations of the retina in immature and mature retinas.
3. The effect of hyperbaric oxygen on the immature and mature retina using the parameters listed under 2 above.
4. The effect of hyperbaric oxygen on the conjunctival and retinal vasculature; pupillary reactions; intraocular pressure; retinal function tests (visual acuity, visual fields, color discrimination, dark adaptometry, electroretinography, and electro-oculography); and intraocular pressure in the normal human eye and in pathologic conditions (senile macular degeneration, drug toxicities, central retinal artery and vein occlusions, uveitis, glaucoma, strabismus, and retinal detachments). In addition to the functional parameters listed above, induced changes in the basic pathologic condition should be noted.

5. Changes induced in the blood-aqueous barrier and the permeability of the eye to therapeutic agents under hyperbaric oxygenation should be studied.
6. Projects to evaluate the present status of individuals afflicted with RLF should be studied from the viewpoint of their: (*a*) Educational opportunities; (*b*) educability; (*c*) social, financial, and psychological needs; (*d*) vocational counseling; and (*e*) occupational status and opportunities.

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Chapter 17—TUMORS OF THE EYE AND ADNEXA

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INTRODUCTION

Ocular tumors are of very special significance, not only because they, in common with many other diseases to be considered in this report, lead to serious visual loss and difficult cosmetic problems, but more importantly because they are ophthalmologically unique: they present the only life-endangering situations with which the ophthalmologist must cope. Often it is extremely difficult or impossible for him to determine the nature of an ocular tumor by clinical methods of examination, and a biopsy may be impossible to obtain. Sometimes it is even impossible to determine whether a tumor is or is not present.

Ocular tumors fall into three main groups: (*a*) The intraocular, (*b*) the external, arising in the lids or conjunctiva, and (*c*) the orbital. Each of these presents the ophthalmologist with different problems in recognition, diagnosis, and management. In some situations, the ophthalmic surgeon must run the risk of a fatal outcome in his effort to minimize visual loss or to avoid a disfiguring operation. In others, he may go to the opposite extreme by performing unnecessarily radical surgery in his effort to fight a possibly lethal cancer.

It is the purpose of this section of the report to summarize the state of our knowledge concerning various aspects of the most important ocular tumors. Attention will be focused on those problems requiring continued clinical and laboratory investigation to improve our understanding of the lesions involved; to facilitate correct clinical and laboratory diagnosis; to achieve better therapeutic results; and to minimize the amount of therapeutic trauma inflicted on the patient in the effort to save his life. This report will not deal with those aspects of the cancer problem which are generally conceded to belong under the jurisdiction of the National Cancer Institute.

RETINOBLASTOMA

Definition

This malignant neoplasm is generally assumed to be congenital, although its presence is usually not recognized until the child is several months to several years of age (*1*). The tumor arises from undifferentiated or very poorly differentiated retinal neuroblasts (the so-called retinoblasts), often in multicentric foci. Both eyes are affected in one-quarter to one-third of the cases.

Incidence

Retinoblastoma is the most frequent malignant ocular neoplasm of childhood. Its frequency has been estimated at 1 in 34,000 to 1 in 14,000 births, and an increase in frequency has been noted between 1925 and 1960 (*2, 3*). Retinoblastomas account for about 20 percent of all eye enucleations in children less than 15 years of age and for almost one-half of the enucleations performed during the first 2 years of life (*4, 5*).

Etiology

While some cases of retinoblastoma are familial, the great majority (94–98 percent) are sporadic. The etiology of the sporadic cases is unknown. The familial cases are almost always the result of an autosomal dominant gene that exhibits variable penetrance (*2, 3*).

This tumor occurs worldwide, affects all races, and shows no sex predilection. In familial cases, the survivor runs the dangerously high risk—a 50-percent chance—of producing affected offspring. In sporadic cases the risk is less—25 percent—but still significant (*2, 3*).

Course

Retinoblastomas originate in the retina, but as they enlarge, they may grow inward toward the vitreous (endophytic type), or outward, producing a subretinal mass that detaches the retina (exophytic type) (*6*). In many cases, the tumor grows in both directions. Typically, the tumor outgrows its blood supply, resulting in large areas of necrosis. Intraocular spread may occur in all directions, but the most important is to the optic nerve; it is via this pathway that the tumor gains access to the sub-

arachnoid fluid and thence to the brain. Invasion of the choroid, ciliary body, iris, or anterior chamber angle is also of grave significance, because these vascular tissues open up avenues for hematogenous dissemination and spread into the orbit (*1, 3, 6*). Spontaneous regression does occasionally occur, but it is very rare.

Prognosis

Prognosis depends on many variables, the most important being the size of the tumor and the extent of its spread when treated. The prognosis has improved greatly during recent years, mainly because cases are being uncovered at a much earlier stage than was possible in the past. Parents and pediatricians are much more knowledgeable today. They generally seek ophthalmologic consultation whenever something seems abnormal about the eyes. Ophthalmologists also have a higher index of suspicion, and in performing enucleations, they have been better educated to obtain a longer segment of optic nerve than was customary in the past. Thus, even if a retinoblastoma has spread into the optic nerve, the situation is not desperate, providing the ophthalmologist has cut the nerve well beyond the tumor.

Retinoblastomas that are confined to the retina and vitreous carry an excellent prognosis, with a cure rate of about 85 percent obtainable by enucleation or radiation therapy. In contrast, invasion of the optic nerve and its meninges up to the plane of surgical transection, massive infiltration of the uvea, or extraocular extension indicate a very poor prognosis. Another, though less important, indicator of prognosis is the degree of differentiation. The more differentiated tumors, containing large numbers of Flexner-Wintersteiner rosettes and few mitotic figures, have a better prognosis than the completely undifferentiated anaplastic tumors that contain large numbers of mitotic figures.

Treatment

Treatment of retinoblastoma presents a therapeutic dilemma: to conserve life without consideration of visual loss by prompt enucleation, or to attempt to conserve vision by treating the tumor with radiation, chemotherapy, and/or photocoagulation. Most ophthalmologists, when faced with a unilateral retinoblastoma, prefer to enucleate the tumor-containing eye. In such cases the remaining eye must be examined periodically because, in some bilateral cases, the tumor in the second eye is so minute and grows so slowly that a period of 1 to 2 years may elapse before its presence becomes recognizable. If both eyes contain large tumors, it is often necessary to enucleate both. If the tumor or tumors are small in one or both eyes, an effort may be made to eradicate the tumor using X-ray, radon seeds, or cobalt-60 applicators, with or without chemotherapy and/or photocoagulation (*1, 8–11*).

A fine historical review of the treatment of retinoblastoma is contained in Dunphy's Jackson Memorial Lecture (*12*).

Problems and Their Study

One difficult problem concerns differential diagnosis. There are a number of lesions that may easily be mistaken clinically for retinoblastoma—for example, Coats' disease, nematode endophthalmitis, persistence and hyperplasia of the primary vitreous, retrolental fibroplasia, and unsuspected ocular trauma, to name a few (*13*). About 8–9 percent of the enucleations performed on children under 15 years of age are for nonneoplastic lesions that are *suspected* of being retinoblastomas (*4*). As a result of many fine clinicopathologic studies, particularly those of Reese and his coworkers, much has been learned about some of the more important "pseudogliomas," as these benign lesions are called, and some needless enucleations for "possible retinoblastoma" are thus being avoided (*14*).

The opposite type of error, while less frequent, is even more serious. When a retinoblastoma is present but not clinically suspected, it may grow so large or spread so extensively before the eye is enucleated that the case becomes hopeless. Again, as a result of clinicopathologic studies, it is becoming better appreciated that, in the differential diagnosis of uveitis, endophthalmitis, cataract, glaucoma, retinal detachment, and intraocular hemorrhage in a child, the possibility of retinoblastoma must always be given serious consideration. In a recent, yet unpublished study at the Armed Forces Institute of Pathology, Stafford and Yanoff found that, in 8 percent of the retinoblastoma cases, enucleation was delayed because the initial clinical diagnosis and treatment were mistakenly concerned with ocular inflammation. Routine ophthalmoscopic examination during the neonatal period would certainly increase the proportion of early, uncomplicated cases and improve the cure rate.

The development of better methods for ophthalmoscopic visualization and photography of retinal lesions would, first, improve clinical diagnosis and, second, facilitate following the course of a lesion, with or without therapy. Binocular indirect ophthalmoscopy is believed by many to have greatly improved clinical diagnosis of retinal lesions; but stereophotographic methods for adequately recording the retinal pictures thus obtained in color must await technical improvement in routine clinical fundus photography. The Donaldson stereocamera

gives a superb stereo retinal picture, and its production should be supported. Fluorescein fundus photography may also prove useful.

Adjunctive methods of diagnosis also need development. The clinical diagnosis of some of the lesions often confused with retinoblastoma (e.g., nematode endophthalmitis) may be exceedingly difficult. Thus, reliable methods (e.g., serologic, skin testing, etc.) for the recognition of *Toxocara canis* infection might be very useful.

It has been shown that children with neuroblastomas excrete increased quantities of homovanillic acid (HVA) and vanillyl-mandelic acid (VMA) in the urine (*15*). Recent work indicates that this may also be characteristic of at least some cases of retinoblastoma (*16*). If this proves to be a very constant finding, then the test could become very useful in differential diagnosis.

Better methods are needed for determining the presence or absence of an intraocular neoplasm, particularly when the media are opaque and the interior of the eye cannot be visualized. Ultrasonography, uptake of radioactive compounds, and X-ray techniques all need improvement.

Another problem concerns the distinction of familial versus sporadic cases. In the absence of a good family history, what is first considered to be a sporadic case may actually be a genetically determined case. The distinction is essential for proper eugenic counseling (*2*). Much information has recently been obtained to provide a better basis for such counseling, but many physicians are still not adequately informed. It is important not only for ophthalmologists and geneticists to be informed, but also for pediatricians and general practitioners to know what to advise survivors and parents of affected children. Obtaining full-family medical histories and carrying out long-term followup of survivors are important pieces of ongoing research that must be encouraged and fostered.

Retinoblastoma is thought to be increasing in frequency (*2*). The question of how much this increase is attributable to the increased number of survivors now producing affected offspring and how much to an increase of mutant genes in the world's population needs more thorough investigation. Such a thorough study should not neglect the possibility of geographic variations that might provide clues as to etiology. In several parts of the world where, due to poverty, ignorance, and inadequate medical facilities, the tumor is almost always fatal and familial cases are, therefore, very rare, retinoblastoma nevertheless seems to occur as frequently or even more frequently than in the United States.

Continuing studies are providing more reliable information on the effectiveness of the various modes of therapy employed. It is still uncertain whether chemotherapy in addition to radiation therapy increases the probability of tumor control in cases considered favorable (*10*). It also remains to be proved whether, in those cases with extensive disease requiring more aggressive therapy, intra-arterial administration of TEM is more effective than the intramuscular route. While TEM is the agent that has had the greatest clinical trial in the treatment of retinoblastoma, it seems likely that newer chemotherapeutic agents such as vancristine and actinomycin D will prove to be even more effective.

One recent author observed that, in a small series of cases treated in part by photocoagulation, there was an apparently greater incidence of choroidal, scleral, and extraocular invasion; this suggests that photocoagulation, by destroying Bruch's membrane, may facilitate choroidal invasion and extraocular extension. Long-term followup studies of successfully treated cases in which large doses of X-ray were used have also revealed many complications—including the late appearance of new malignant neoplasms in the irradiated tissues (*17*). Such careful studies have led to marked changes in radiation dosage. The development and evaluation of new chemotherapeutic agents, including use of intra-arterial routes of administration (particularly for advanced cases), will offer much needed alternatives or adjuncts to the use of X-ray and photocoagulation.

Greater experience in the use of bone-marrow biopsies and better detection of tumor cells in the aqueous humor and peripheral blood are needed; preliminary studies suggest that these methods may be useful in evaluating prognosis and establishing indications for intensive chemotherapy.

Retinoblastomas have been maintained in tissue culture, and this tissue has been used for the in vitro study of *Toxoplasma gondii* (*18*). The same investigators are attempting to adapt the cultured retinoblastoma to fetal animals (*19*). If successful, this might provide a useful method for the in vivo study of therapeutic agents.

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MALIGNANT MELANOMAS

Definition

This is a group of malignant neoplasms arising from cells, located in the uveal tract, that can produce the pigment melanin. Great variations exists in the amount of pigment produced, and completely nonpigmented melanomas are not rare. Bilaterality and the occurrence of more than one tumor in an eye are very rare.

Incidence

The frequency of uveal melanomas among ophthalmologic patients has been reported to range from 1 to 7 per 10,000 (*20*). Denmark, during the period 1943–52, recorded an average of 30 new cases each year, an incidence of one malignant uveal melanoma per year for every 1,356,000 people (*20*).

The prevalence of malignant melanomas varies markedly with age and race, but only slightly with sex. It is a very rare tumor in infants and small children. In a series of 3,628 cases in which the patient's age at the time of enucleation was known, only four were in the first decade and only 22 were in the second decade (*21, 22*). Two-thirds of the patients were more than 50 years of age. The clinical manifestations and behavior of malignant melanomas of the uvea in children are similar to those in adults (*23*). Melanomas of the uvea are rare in non-Caucasians of all ages; this ocular tumor, therefore, is rarely seen in Africa, Asia, India, or parts of South America (*24, 25*). On the other hand, in Europe and the United States, malignant melanoma is the most common of all intraocular neoplasms. It accounts for almost 10 percent of enucleations regardless of age and for a considerably larger proportion of enucleations in the older age groups (*21, 26*). There is a slight preponderance of males in most reported series, though some reports have indicated a preponderance of females (*20*).

Etiology

Relatively little is known about the precise cause of malignant melanomas. The rarity of the neoplasm in prepubertal children suggests a hormonal factor. And its rarity in non-Caucasians suggests a genetic factor; but, on the other hand, the familial occurrence of malignant melanoma is also extremely rare (*27, 28*). At least three predisposing conditions are known: von Recklinghausen's neurofibromatosis, congenital melanosis (ocular melanocytosis and oculodermal melanocytosis), and nevi (benign melanomas) of the uvea. The latter are believed to be the most important (*29*).

Course

Malignant melanomas of the uvea are a group of neoplasms exhibiting a broad spectrum of biologic activity. Some of these tumors are well known to be highly malignant, exhibiting great propensity for vascular invasion and hematogenous dissemination; for this reason, the entire family of melanomas has acquired an undeservedly bad reputation. In recent years, considerable attention has been given to the other end of the spectrum, and it is becoming more generally appreciated that many uveal melanomas are very slow growing and essentially nonmetastasizing. Unfortunately, the ophthalmologist has no certain method for determining, by clinical examination alone, at which end of the spectrum of biologic behavior a given tumor might belong. It has, therefore, been customary in ophthalmologic practice to treat radically, usually by enucleation of the eye, as soon as a uveal melanoma is discovered. For this reason we have an appalling lack of knowledge about the natural behavior and clinical course of malignant melanomas, particularly those of the posterior uvea. Moreover, there is seldom any way for the patient or the ophthalmologist to know how long the tumor had been present before its discovery.

There are a few exceptions to these statements.

In some cases, the ophthalmologist or the patient has decided against enucleation and, consequently, it has been possible to follow the course of the tumor. Surprisingly, in several such cases, the tumor grew only slowly, and the patient eventually died of some other, unrelated condition.

The most noteworthy exception concerns tumors of the iris. These are situated so that the patient often knows how long a lesion has been present, when it started to grow larger, how rapidly it grew, and when it started to produce symptoms. These tumors also can be examined and photographed more satisfactorily than those in other locations, and they can be treated less radically by iridectomy. Thus melanomas of the iris are now recognized to be very low-grade tumors (*27, 28, 30–32*). They do have the capacity for slow, progressive growth; they may cause a number of serious ocular complications (e.g., hyphema, glaucoma, cataract, etc.); they will recur if incompletely excised; and they may even produce extraocular extensions. But the important lesson that has been learned is that they rarely metastasize and kill the patient.

While little is known about the rate of growth of melanomas of the posterior uvea, pathologic examinations have clearly demonstrated their many patterns of growth. The one most frequently observed is toward the vitreous. The melanoma tends to grow as a bulky mass, bulging inward and elevating the retina. Bruch's membrane often gives way, so that the tumor mushrooms through into the subretinal space, causing considerable retinal detachment. It may also invade the retina or even infiltrate through it into the vitreous.

A much less frequent manner of growth is a diffuse spread through the uvea and into the scleral canals along ciliary vessels and nerves and along vortex veins; there is no significant elevation of the retina in this case. Various combinations of these two growth patterns are observed.

While spread into the optic nerve does occur, it is a much less significant route of dissemination than in the case of retinoblastoma. Melanomas tend to invade blood vessels and to become disseminated hematogenously. They also infiltrate through the sclera into the orbit.

Malignant melanomas are sometimes discovered in the course of a routine eye examination, before they have produced symptoms. Much more frequently, the tumors cause secondary changes that are responsible for the symptoms that bring the patient to the ophthalmologist. These include retinal degeneration, retinal detachment, intraocular hemorrhage, glaucoma, cataract, endophthalmitis, panophthalmitis, and uveitis. It is apparent, therefore, that an intraocular neoplasm must be considered in the differential diagnosis of many of the most important conditions that cause unilateral blindness.

Prognosis

Prognosis depends on many variables, the most significant being the biologic activity of the tumor. Many years ago Callender showed that, by histopathologic study, uveal melanomas could be classified cytologically in such a way that their prognosis could be estimated (*33*). His classification is still in vogue because it has proven so useful (*21*). Those melanomas composed almost entirely of spindle cells have a much better prognosis than those that contain a large admixture of epithelioid cells. Among the pure spindle cell melanomas, those whose cells have uniform slender nuclei without nucleoli and with rare mitotic figures are almost always benign. Less than 20 percent prove fatal within 15 years after enucleation (*21*). At the opposite end of the spectrum, the pure epithelioid cells tumors exhibiting much pleomorphism and considerable mitotic activity are highly malignant. More than half the patients succumb to their tumors within 5 years after enucleation (*21*).

Other very significant factors include the size of the tumor, extraocular extension, and vascular invasion. Small melanomas have a much better prognosis than large ones (*34*). Tumors that have extended out of the globe into the orbit have twice as high a 5-year mortality rate as those that have not done so, and their rate of orbital recurrence after enucleation is 26 times greater (*35*).

Of comparatively less prognostic significance are the patient's age (young patients fare better than old) and sex (insignificantly better for women), and the tumor's degree of pigmentation (slightly better for amelanotic than for very heavily pigmented tumors), and reticulum content (better for those with a stroma containing a dense network of reticulin fibers) (*21*).

Iris tumors have a more favorable prognosis than those of the posterior uvea, but the comparison is not entirely fair, because they are almost always very much smaller than those of the choroid and ciliary body at the time of treatment.

Treatment

For many years, enucleation was the only treatment generally advocated for malignant uveal melanomas. During recent years, iridectomy has become widely accepted as the treatment of choice for resectable iris tumors (*27, 30, 32*). More recently ophthalmic surgeons have devised new operations for segmental resection of localized tumors involving the ciliary body (*36–39*). The immediate results have been encouraging, but the total number of cases

treated and the length of postoperative followup are not yet sufficient to permit evaluation.

No serious efforts have been made to resect choroidal melanomas, and almost everyone is in agreement that the treatment of choice for these tumors is enucleation of the eye. The only exceptions are small lesions (1 to 4 disc diameters in size) that have not led to any significant complication in eyes with good vision. Some authorities recommend no therapy at all in such cases, unless repeated observations indicate growth and progressive functional change (*26*). When and if it is decided to treat the lesion, several methods are available: Diathermy, photocoagulation, cobalt-60 applicators, and radon seeds (*27, 40, 41*). Cryosurgery has not yet been evaluated.

In those advanced cases showing preoperative evidence of orbital invasion, exenteration is indicated, providing that thorough clinical and radiologic study fails to demonstrate signs of metastatic disease. On the other hand, if evidence of extraocular extension is so minimal that it is discovered only at the time of enucleation or later, upon histopathologic examination of the enucleated eye, then the question of what should be done is very controversial (*27*). Some believe that exenteration is indicated (*35*), while others believe that there is little to be gained by such a radical procedure (*42*). The value of radiation and/or chemotherapy in such cases remains to be established.

Problems and Their Study

Accurate diagnosis of intraocular melanomas is frequently difficult and often impossible. About 10 percent of melanomas arising in the choroid and ciliary body are unsuspected, mainly because the media are opaque and the interior of the eye cannot be visualized (*43*). In these cases, it is only after the eye is enucleated because of pain due to glaucoma and/or inflammation that the tumor is discovered in the pathology laboratory.

Even when the media are clear, the correct diagnosis is often not made preoperatively. In a study of 204 eyes that were enucleated after one or more operations for retinal detachment, 60 were found to contain intraocular tumors that had not been recognized at the time of retinal surgery (*44*). Of the 60 tumors, 56 were malignant melanomas.

Errors are also made in the opposite direction. Ferry (*26*) found that almost 20 percent of 529 posterior lesions visible by ophthalmoscopy through clear media were not malignant melanomas as they had been thought to be prior to enucleation. Serous and hemorrhagic detachments of the retina, retinal pigment epithelium, choroid, and ciliary body; inflammatory lesions; and benign tumors of the uvea and optic disc accounted for most of these erroneous diagnoses of malignant melanoma.

There is evidently much room for improvement in clinical diagnosis, and considerable effort is being made in this direction. In eyes with opaque media, which cannot be adequately examined by ophthalmoscopy, ultrasonography (*45*) and the uptake of radioactive test substances (*27, 46–48*) have potential value; but better instrumentation and more experience with these techniques will be required before they can be adequately evaluated. The P_{32} test (*46*) is most useful when the counter can be placed directly over a questionable lesion; but in the case of eyes with opaque media, the chances of placing the counter in the most suitable position are small. The development of more sensitive devices and scanning techniques should prove useful in such cases.

In the case of small posterior lesions observed through clear media, many experienced clinicians are of the opinion that binocular indirect ophthalmoscopy and slit-lamp examination, if carefully done by well-trained observers, will permit differential diagnosis between malignant melanomas and the many posterior polar lesions that are so often confused with them (*28, 31, 49*). It is apparent, however, that many errors are being made, and that better training in the use of binocular ophthalmoscopy, biomicroscopy, retroillumination, and transillumination is needed. The newer methods of fluorescein fundus photography (*49, 50*) should also be useful, particularly in the identification of nevi and subretinal hemorrhages. Much more experience is needed, and better techniques will be required in the difficult differentiation among metastatic carcinomas, hemangiomas, and melanomas. Better methods of recording the changes occurring in fundus lesions stereoscopically, by color fundus photography, would be very helpful in deciding whether a given lesion's course suggested benign or malignant activity. The uptake of tetracyclines and other fluorescent compounds by melanomas may prove useful (*47*).

In those cases presenting difficulties in differential diagnosis between serous retinal detachment and tumor, improved methods of transillumination, both preoperatively and during surgery (after transection of one or more extraocular muscles), should reduce the number of errors. Safer, more satisfactory methods of obtaining biopsy specimens of choroidal masses, perhaps with the aid of cryocoagulation to prevent dissemination of tumor cells into the orbit, would be most helpful.

Much more basic information concerning the epidemiology, histogenesis, and natural history of malignant melanomas must be gathered. There is considerable evidence that malignant melanomas of the uvea arise from preexisting nevi ("benign melanomas"). Unfortunately there is very little infor-

mation concerning the frequency of choroidal nevi and their natural histories, although a recent study of normal adult eyes obtained post mortem revealed them to be present in 9 percent of 100 patients (*51*). This is a much higher incidence than previously reported from clinical studies. What variations in the incidence of nevi exist with different age and racial groups, with variations in pigmentation of skin, hair, and eyes, and in relation to geographic factors remain to be determined. The results of one study suggest that uveal melanomas occur more frequently in patients whose irises are lightly pigmented (*20*).

When a small melanoma is discovered, what can be predicted about its behavior? How long will it take to cause retinal detachment or other serious ocular complications? How long can it be followed without fear that metastasis will occur? Is there any certainty that enucleation increases longevity, and how does the effectiveness of enucleation vary with the size of the tumor? These are questions that cannot be answered until we know more about the natural history of these tumors (*52*). There is a genuine need for a Registry of Untreated Melanomas, national in scope, from which some answers to the foregoing questions might be obtained. It should be mentioned here that, while almost every ophthalmologist recommends enucleation of the eye as the routine procedure for melanomas of the choroid and ciliary body, many wonder just how many patients benefit by the operations. With the large percentage of errors in diagnosis and the knowledge that 20–70 percent of all patients (depending on the cell type of their tumors) eventually die of metastatic disease in spite of enucleation (*21*), there is, indeed, reason to question the standard practice of enucleation. The potential value of such a registry has recently been demonstrated in a study of melanotic tumors of the optic disc. Once thought to be malignant, these are now known to be benign (*53*). The American Academy of Ophthalmology and Otolaryngology is interested in establishing a National Registry of Untreated Uveal Tumors, but the undertaking is a large one; it will require long-term financial support, as well as widespread cooperation of participating centers, referring physicians, and patients.

Development of a good experimental model of the uveal melanoma would permit more scientific study of the uptake of various radioactive substances, phenothiazines, and fluorochromes for the development of diagnostic tests and for the testing of various therapeutic measures. No natural model is presently available, though Dr. Robert P. Burns and coworkers (*54*) at the University of Oregon have used the transmissible malignant melanoma of the Syrian golden hamster to evaluate enucleation and other forms of therapy. While their studies indicate that both enucleation and radiation favorably influence the course of this transmissible tumor, a naturally occurring uveal melanoma or one induced by a carcinogenic agent would provide a better model for evaluation of therapeutic measures, including lasers, cryocoagulation, and so on.

There is no satisfactory treatment for the advanced stages of this malignant disease. Effective chemotherapeutic agents need to be developed, perhaps taking advantage of the affinity of these tumors for certain radioactive materials, fluorochromes, and phenothiazines (*47, 48, 55, 56*).

As was indicated previously (see "Treatment"), the effectiveness of the new surgical procedures devised by Muller (*36*), Stallard (*37*), and others (*38, 39*) for the excision of ciliary body tumors and melanomas of the iris that have invaded the chamber angle will not be known for quite some time. Greater numbers of patients will have to be followed for much longer periods of time to permit an adequate appraisal.

Fundamental studies of the body's immune response to malignant melanomas would seem to be of great potential significance. It is a well-recognized clinical observation that patients who have seemingly been cured by enucleation of the eye may remain in excellent health for many years, yet eventually die of widespread metastatic disease. Obviously, the ocular melanoma must have metastasized prior to enucleation, yet the disseminated neoplastic cells remained dormant. Is this long latent period the result of an immunologic suppression of the tumor cells? If so, what finally enables the neoplasm to break through? How can the body's immunologic mechanisms be stimulated to keep the tumor permanently suppressed? Does immunologic suppression account for all permanent cures? Does removal of the primary intraocular tumor affect the body's immune response favorably or unfavorably? Very little work has been done to provide answers to these questions.

How frequently does extraocular extension and vascular invasion really occur? Is it as infrequent as most clinicians assume, or is it much more frequent, as some pathologists believe? If it is quite common, is this an indication for more radical surgical management (exenteration of the orbital contents)—or should it, perhaps, be considered a reason for abstaining from surgery altogether?

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METASTATIC TUMORS

Types

While almost any neoplasm may metastasize to the eye, carcinomas are the only ones that do so with sufficient frequency to constitute an important ophthalmologic problem (*57, 58*). Metastatic sarcomas, melanomas, and lymphomas are all exceedingly rare in the eye. Leukemic infiltration of the uvea and retina is observed rather frequently post mortem (*59*), especially in acute leukemias, but ocular involvement is usually a terminal event that does not constitute a diagnostic or therapeutic problem (*60*).

Incidence

Ophthalmologists and ocular pathologists encounter metastatic carcinoma much less frequently

than primary malignant melanoma of the uvea. Hart found only 133 cases on file in the Registry of Ophthalmic Pathology in comparison with about 4,000 uveal melanomas. This, however, does not reflect the true incidence, for there are undoubtedly many cases that develop terminally and many others that are recognized clinically but not referred to an eye hospital.

At the Institute of Ophthalmology in London, Greer reported that there were 45 cases of metastatic carcinoma during a 19-year period; during this same period, there were 236 cases of retinoblastoma and 1,274 of malignant melanoma of the choroid (*61, 62*). Many experienced clinicians are of the opinion that metastatic carcinoma presents a much more frequent and important problem than is generally recognized.

Certain carcinomas are especially prone to metastasize to the eye: mammary carcinomas in women and bronchogenic carcinomas in men. The former outnumber all others by about two to one. Why breast carcinomas exhibit such a propensity for spread to the eye is unexplained. Metastasis from the breast to the eye usually occurs several months to several years after mastectomy. Bilaterality is observed in about 20–25 percent of these cases, although usually only one eye is involved at the time of onset of symptoms (*62*). In women, the ocular metastasis is rarely the initial complaint. On the other hand, in the case of men's bronchogenic carcinomas that metastasize to the eye, the ocular metastasis is often the first indication that the patient has a malignancy.

Metastatic carcinomas are found mainly in the choroid posteriorly, while metastasis to the iris, ciliary body, or retina is rarely observed (*57, 62*). When the iris and/or ciliary body is involved, the resultant clinical picture is often that of a peculiar uveitis with or without secondary glaucoma.

Prognosis

As might be expected, ocular metastasis of a carcinoma always carries a grave prognosis. If the patient is studied very carefully, evidence of other metastases will usually be found either at the time of enucleation or soon afterward. Rarely is the ocular lesion the only metastasis, and only in such rare cases can one expect to obtain a cure by enucleation.

Treatment

In the presence of other evidence of metastatic disease, the ocular lesion is treated in conjunction with treatment of the extraocular lesions (e.g., by hormone therapy, castration, adrenalectomy, radiation, etc.) (*64*). X-ray therapy will often improve the visual status, though it may not permanently control the ocular metastasis. If thorough study reveals no evidence of other metastases, then one must consider the possibility that the introcular tumor might be a primary malignant melanoma rather than a metastatic carcinoma and consider enucleation of the eye. X-ray therapy might also be tried; if a prompt response is obtained, this would be more consistent with the behavior of metastatic carcinoma.

Ordinarily, enucleation of the eye is not recommended for metastatic carcinoma unless there is some additional indication (e.g., pain from uveitis or secondary glaucoma).

Problems and Their Study

The most important problem is that of correct diagnosis. A patient with a past history of carcinoma who develops a choroidal mass is quite properly suspected of having a metastasis; but, if there is no other evidence of metastatic disease, consideration must also be given to the possibility that the choroidal tumor may be a melanoma, a hemangioma, a disciform degeneration, or some other simulating lesion. Better clinical and laboratory diagnosis is necessary—a need already stressed in the discussion of malignant melanomas of the uvea (see sec. 1B).

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ANGIOMATOUS TUMORS

Cavernous Hemangioma of Choroid

Angiomatous tumors of the anterior uvea are exceedingly rare. The cavernous hemangioma of the choroid is important, however. It occurs mainly at the posterior pole, where it eventually leads to degenerative changes in the overlying macula. In some cases, it is associated with various components of the Sturge-Weber syndrome (ipsilateral "port wine" facial and meningeal hemangiomas, and glaucoma). In the absence of these features, the choroidal hemangioma is often mistaken for a malignant mel-

anoma. As a matter of fact, many experienced clinicians are of the opinion that the choroidal hemangioma is the most difficult lesion to differentiate from a placoid posterior polar melanoma. The two tumors produce similar changes in the overlying retina, have a similar ophthalmoscopic appearance, and cannot be differentiated satisfactorily by the use of intravenous fluorescein.

These lesions should, theoretically, be easy to differentiate by use of various radioactive substances, fluorochromes, or phenothiazines that are taken up by melanomas but not by hemangiomas. But, because of the characteristic location of the cavernous hemangioma at the posterior pole, and because of the comparatively small size of the lesion, there have been great technical difficulties in achieving this theoretically possible goal. Better instrumentation and newer methods should overcome these difficulties.

The treatment of cavernous hemangiomas has been notoriously unsuccessful. Methods are needed to effectively prevent the retinal degeneration and detachment that seriously impair vision in eyes containing these otherwise benign, innocuous tumors. Photocoagulaton has been found to be very useful in this respect, but greater experience and longer periods of followup will be necessary before its use can be fully evaluated.

The discovery of a choroidal hemangioma or any posterior polar placoid mass should stimulate the ophthalmologist to search carefully for a facial hemangioma, which sometimes, especially in dark-complexioned individuals or in women who use cosmetics to hide the lesion, may not be readily detected. In every case in which an ipsilateral facial angioma is present, a search should also be made for evidence of an intracranial tumor.

Angiomatosis Retinae

This is a peculiar angioblastic malformation of the retina known as von Hippel's disease. When associated with similar vascular tumors of the cerebellum, the condition is called the von Hippel-Lindau syndrome. The retinal tumor is usually situated at the periphery, and large tortuous feeding vessels pass to the tumor from the disc. Clinical diagnosis is usually not difficult if the eye is examined before extensive retinal detachment has occurred. The main problem clinically is the control of the lesion to prevent progression with consequent retinopathy and detachment. Localized lesions are effectively treated by light coagulation, diathermy, or cryosurgery, while extensive areas of angiomatosis retinae are treated by X-ray (*65*).

The finding of angiomatosis retinae should always prompt the ophthalmologist to take a very careful family history. Many familial cases have been overlooked because nobody had pieced together the entire picture. One member of the family may have had an eye removed for unknown reasons, another may have a brain tumor, and so on.

Coat's Disease

Telangiectasia of the retina leading to an exudative retinopathy and subsequent formation of large, dark bullous areas of retinal detachment is called Coat's disease (*65*). This disorder is of great significance for two reasons: (1) Since it is found mainly in children, it is one of the many intraocular lesions that is mistaken for retinoblastoma; and (2) because the lesions often involve much of the retina and lead to extensive areas of detachment, severe visual impairment may ensue.

According to Reese (*65*), radiation is of no help, but light coagulation or diathermy are effective for localized lesions. Cryosurgery needs to be evaluated.

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TUMORS OF THE EYELID

Basal Cell Carcinoma

This very prevalent cancer has a special predilection for the face, and the eyelids are very frequently involved. It is the most common malignancy with which the ophthalmologist must deal; it accounts for 90 percent of all malignant tumors on the lids (*66–68*). The lower lid and inner canthus are the most frequent sites, accounting for 80 percent of basal carcinomas on the lids (*68*). With only rare exceptions, the tumor arises from the cutaneous surface of the lids, and the conjunctiva is involved only secondarily by direct extension.

Basal cell carcinomas are invasive cancers, but they do not metastasize hematogenously or via lymphatics. In most other anatomical sites, they pose no great therapeutic problem; they can be widely excised or radiated without difficulty. On the lid, and particularly at the inner canthus, it is often extremely difficult to completely remove an invasive basal cell carcinoma without considerable functional damage requiring plastic repair. Radiation therapy requires careful protecton of the eye while the lid lesion is being treated.

There is considerable controversy between surgeons and radiologists as to whether basal cell carcinomas should be treated surgically or by irradiation (*69*). The vast majority can be controlled by either method, and except in badly neglected cases, there should be no mortality The debate concerning proper therapy is centered about the problem of

preservation of function and achieving a good cosmetic result. While radiation is generally less traumatic and preferred by most patients, it is not without complications. Even the most skilled and experienced radiotherapists report such complications as keratinization of the cornea, keratitis, corneal ulcers, cataracts, and skin necrosis in 10 percent of their cases (*69*).

Squamous Cell Carcinoma

Squamous cell carcinoma, while much less common on the skin than basal cell carcinoma, is potentially more important because, in addition to its invasiveness, the tumor has the capacity to invade lymphatics and blood vessels. Formerly squamous cell carcinoma was thought to occur fairly frequently on the lids, and about 5–10 percent of lid tumors were thought to be squamous cell cancers. During recent years, however, a number of pseudocancerous lesions have been recognized (*vide infra*). These were formerly labeled by most pathologists as squamous cell carcinomas. As a result of these advances in histopathologic diagnosis of lid lesions, it is now becoming more generally appreciated that squamous cell carcinoma is a rather rare tumor of the lid, accounting for less than 3 percent of its malignant neoplasms (*70*).

There are a number of precancerous lesions (e.g., senile keratosis, Bowen's disease, xeroderma pigmentosum, etc.) that occur on the lids. Prophylactic removal of these would reduce the number of invasive squamous cell cancers. As in the case of basal cell carcinomas, there is no agreement as to whether surgical excision or radiation therapy is the treatment of choice.

Pseudocancerous Lesions

During recent years pathologists have delineated a number of cutaneous lesions that had formerly been mistaken for squamous cell carcinoma. Interestingly, many of them have a predilection for the face, and involvement of the eyelids is frequently observed. Some of the more important examples are keratoacanthoma, inverted follicular keratosis, pilomatrixoma (also called benign calcifying epithelioma), senile keratosis, seborrheic keratosis, and pseudoepitheliomatous hyperplasia (*66, 69, 70*). The sudden onset and very rapid growth of a lesion on the eyelid should suggest one of these noncancerous lesions; true squamous cell carcinomas generally progress much more slowly. Several of these benign lesions are suspected of being viral tumors but satisfactory proof is lacking. This would seem to be an area that might prove fruitful for virologic investigation.

The fact that these pseudocancerous lesions are so much more frequent on the lid than squamous cell carcinoma needs to be more widely recognized. The majority can be managed much more conservatively than true cancerous lesions.

Miscellaneous Malignant Tumors

The eyelids contain a variety of tissues from which malignant neoplasms may rise. The only two beside basal cell and squamous cell carinoma that are encountered with any regularity are malignant melanomas and sebaceous carcinomas. Each of these accounts for about 1 percent of eyelid malignancies.

Malignant melanoma of the skin is generally considered a very highly malignant neoplasm. Its prognosis is much worse than that of melanomas of the conjunctiva or uveal tract. While many of those arising in the skin of the lids are also highly malignant, there is one type that carries a more favorable prognosis. This is the melanoma that arises in the "melanotic freckle of Hutchinson," a lesion encountered mainly in older patients (*71*). Here again is a lesion with a predilection for the face and frequent involvement of the eyelids. Simple excision is sufficient for this tumor. For the more highly malignant melanomas, exenteration of the orbit is often recommended (*68*). Resection of the parotid gland and preauricular lymph nodes, combined with a radical neck dissection must be considered since involvement of the regional lymphatics occurs so frequently. To date, there is inadequate information available to judge how these tumors are best treated.

Sebaceous gland carcinomas usually arise from the meibomian glands, but they also may arise from the Zeis glands and the other pilosebaceous elements of the lids. These carcinomas are locally invasive, sometimes involving the lid rather diffusely, and they also invade lymphatics and become disseminated hematogenously.

Those arising from the meibomian glands are often mistaken for chalazia, and treated accordingly. Only after one or more recurrences is the possibility of a malignancy suspected in such cases and a specimen obtained for histopathologic study. Once the diagnosis is established, treatment usually consists of wide local excision. There is insufficient information available for determniation of prognosis and proper treatment.

Angiomas

Angiomatous lesions of the eyelid may be congenital or acquired. The former are by far the most important. Two main varieties are of special significance to ophthalmologists. One is the diffuse dark "port wine" hemangioma (nevus flammeus); the

other is the hemangioendothelioma. The former is of importance mainly because it indicates the possibility of the Sturge-Weber syndrome and calls for thorough evaluation of the ipsilateral eye for glaucoma and/or a choroidal hemangioma. It also presents a cosmetic problem.

The hemangioendothelioma of the newborn often presents a frightening picture of a rapidly growing, seemingly malignant, neoplasm. Reese (*68*) observed that these tumors were more prevalent in premature babies treated with excessive amounts of oxygen during the "retrolental fibroplasia era" and that there was an inverse relationship between the incidence of these vascular lesions and the infant"s birth weight. Reduction in concentration of the oxygen to premature babies coincided with a decline in the incidence of hemangioendotheliomas of the skin. These observations suggest a common pathogenetic relationship between retrolental fibroplasia and hemangioendotheliomas.

Because of the alarming appearance of these tumors and their occurrence in vital areas, including the eyelids, nose, and lips, attempts have been made to control their growth by use of various physical and chemical methods (e.g., freezing, radiation, and sclerosing solutions). Often these agents led to severe secondary effects on the skin and subcutaneous tissues. During recent years, it has become increasingly apparent that the vast majority of these tumors regress spontaneously and that the end result without therapy is almost always better than attempting treatment. Regression usually begins before the infant is 1 year old and, in the majority of cases, is complete by the time the child is 5 (*72*). Tissue culture experiments using varying degrees of oxygenation, including hyperbaric oxygen, might provide interesting information about the various types of vascular tumors.

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CONJUNCTIVAL TUMORS

Squamous Cell Carcinoma

Invasive squamous cell carcinoma arises mainly near the limbus, temporally or nasally. In the United States it is a rather rare tumor, but recent observations suggest that, in other parts of the world (e.g., Africa, Haiti, and Pakistan), it may be more common (*73*). Furthermore, while in the United States carcinomas of the bulbar conjunctiva are observed mainly in older patients, many of the cases observed in Africa, Haiti, and Pakistan involve younger subjects. These geographic variations may well provide clues as to pathogenesis (e.g., racial or genetic factors, environmental stimuli, diet, customs involving use of carcinogenic agents, etc.).

In general these epibulbar tumors grow in an exuberant exophytic (fungating) fashion and tend to become quite large before invading the deeper tissues (*74, 75*). Eventually they invade the globe and orbit and may also metastasize via lymphatics and hematogenously. Fatalities are, however, quite rare in this country. No followup data are available for the cases observed in Africa, Haiti, and Pakistan.

A naturally occurring squamous carcinoma that is remarkably similar to the conjunctival cancer of man is so very prevalent in cattle that it is of considerable economic as well as scientific importance (*76*). The condition has afforded an opportunity to make studies that have a direct bearing on the human cancer. As in man, the "cancer eye" of cattle usually develops at the limbus, progressing through four stages: (1) A precancerous acanthotic leukoplakic lesion, (2) papillary hyperplasia, (3) carcinoma in situ, and (4) invasive cancer. The in situ cancer may also develop in the leukoplakic stage without the formation of an exophytic papillary mass. Also similar to the situation in man is the fact that lesions confined to the limbus carry a much better prognosis than those involving the fornical or bulbar conjunctiva.

It is conceivable that the same etiologic factors that account for the prevalence of cancer eye in cattle might be responsible for the frequency of squamous carcinomas of the conjunctiva in Africa, Haiti, and Pakistan. In this connection, however, it is interesting to note that, in cattle, there is an inverse relationship between pigmentation and the development of squamous carcinoma. According to Anderson (*77*), since a genetic basis exists for the degree of ocular pigmentation and since the presence of pigment in the skin and conjunctiva protects these tissues against cancer, there is reason to believe that genes indirectly determine susceptibility. Ultraviolet light is believed to be at least one important environmenal factor responsible for these tumors (*78*). Since

the tumors observed in the specimens from Africa, Haiti, and Pakistan were obtained from non-Caucasian patients, one must assume that in man, hyperpigmentation does not have the protective effect that it apparently has in cattle.

Carcinoma in Situ

Intraepithelial cancerous lesions are observed much more frequently in the bulbar conjunctiva and limbal epithelium than are invasive cancers. These give rise to leukoplakic areas, but not all leukoplakic lesions are intraepithelial cancers (*74, 75, 76, 79*). For this reason, "leukoplakia" is a term that should be used only for clinical descriptions, not for histopathologic diagnosis. The eponymic designation "Bowen's disease" is also inappropriate for these conjunctival lesions for three reasons: (1) Bowen's disease is a distinctive cutaneous disorder; (2) in many instances the microscopic picture bears little or no resemblance to that of Bowen's disease; and (3) even in those cases that do resemble Bowen's disease microscopically, there are other characteristics of that disease that are not observed in the conjunctival lesions.

Usually these intraepithelial lesions can be safely excised in a conservative manner without interfering with vision. Even when there is extensive involvement of the cornea, t is usually possible to remove the affected epithelium without injuring the deeper tissues of the cornea. Beta radiation, or, if the patient already has a cataract, X-ray therapy, is also a very effective method of controlling these lesions (*80*). Recurrences are not uncommon, but evolution into an invasive lethal cancer is very rare (*73, 74, 79*).

Sometimes these intraepithelial tumors grow as exuberant exophytic papillary masses that may appear much worse clinically than they really are. It has been suggested that, even in these cases, excision of the tumor rather than enucleation of the eye should be attempted.

Pseudocancerous Lesions

Noncancerous leukopakic lesions and acanthotic plaques are also encountered, almost always at the limbus. Irritated pingueculae and pterygia often give rise to pseudoepitheliomatous hyperplasia of the overlying epithelium. Granuloma pyogenicum following excision of a neoplastic lesion may be confused clinically with recurrent cancer. Recently a few pseudoepitheliomatous lesions similar to keratoacanthoma of the skin have been observed on the bulbar conjunctiva (*74*).

Nevi

Pigmented and nonpigmented nevi occur on the bulbar conjunctiva. Typically they are noted early in childhood, but they may enlarge or become more pigmented at puberty or later. Conjunctival nevi are small, fairly discrete, slightly elevated lesions often containing solid or cystic inclusions of conjunctival epithelium within the subepithelial portion of the nevus. They are subject to irritation by the blinking eyelids and, because of the attendant inflammation, they may become painful and seem to enlarge. Malignant change is rare.

Nevi are excised mainly because they are a source of irritation and constitute a cosmetic problem. Some authorities also believe that, since they are a potential source of malignant melanoma, all nevi on or about the eyes should be excised before puberty (*81*). This attitude is based on the knowledge that malignant change before puberty is almost unknown, coupled with the belief that hormonal stimulation during puberty or later may be an etiologic factor in the pathogenesis of malignant melanoma.

Acquired Melanosis

This, in contrast to nevi, is an acquired pigmentation of the conjunctival epithelium that usually appears insidiously in adults. Typically, it spreads slowly, often involving the corneal epithelium peripherially. It may wax and wane spontaneously. The process is intraepithelial and, in the absence of malignant change, causes no significant tumefaction. Reese (*81, 82*) has designated this condition as "precancerous melanosis" because of its potential for evolving into a malignant melanoma; however, Zimmerman (*83*) has pointed out that, in many instances, neither the clinical nor the histopathologic picture is sufficiently disturbing to warrant the term "precancerous." He has herefore advocated the designation "benign acquired melanosis" for such lesions.

Reese formerly believed that almost all conjunctival melanomas arose from precancerous melanosis and that the latter condition should therefore be treated by radiation in order to prevent the progression into cancerous melanosis. Lederman (*84*) is of the opposite opinion—that the nonmalignant stage should not be treated by radiation. He reserves the use of radiation therapy for cancerous melanosis. Reese, on the other hand, prefers to treat the latter condition by exenteration.

If Lederman is correct, his method of treating cancerous melanosis would certainly be preferred to exenteration. There are several problems that make comparisons difficult. Most important is correct diagnosis. Acquired melanosis appears to progress through several stages: benign pigmentation, pigmentation plus junctional activity, in situ malignant melanoma (superficial malignant melanoma), frank

malignant melanoma (*83*). Interpretation of where a given biopsy specimen should be placed in this spectrum of stages is often difficult. Furthermore, a given biopsy specimen is not always representative, for different foci within the areas of acquired melanosis may reveal considerably different degrees of disturbance.

There is need here for a cooperative study with a panel of pathologists to reevaluate pretreatment biopsy specimens and establish uniform criteria for histopathologic diagnosis. Once this has been accomplished, we will be better able to compare various methods of management, providing, of course, that adequate followup data are also available.

Malignant Melanoma

Malignant melanoma of the conjunctiva is rather rare. Melanomas of the uvea are seen 25 to 50 times more often than those of the conjunctiva. They arise from nevi, within areas of acquired melanosis, or in apparently normal conjunctiva. In the past, it was believed that virtually all arose from areas of precancerous melanosis, but it is now agreed that melanomas arising de novo and those originating in nevi are proportionately much more common than was formerly believed. Unpublished observations suggest that melanomas of nevus origin are not only encountered just as often as those arising in acquired melanosis, but that the former have a more favorable prognosis. They generally occur at the limbus, and limbal tumors of all types appear to spread less rapidly than those arising in the fornical or palpebral areas.

How to manage limbal melanomas is controversial. Reese has urged exenteration, while Lederman believes there is a place for radiation therapy. Zimmerman has been impressed by the fact that simple excision of the tumor, particularly in the case of pedunculated limbal melanomas arising de novo or from nevi, has been curative in a remarkable number of cases. These differences of opinion indicate the need for a collaborative study of the problem. Few centers have a large enough series of well-documented cases with good pretreatment biopsy specimens and long posttreatment followup data to permit evaluation; hence the need for a cooperative study with a pooling of cases.

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ORBITAL TUMORS

Types

There are a great number of lesions of various types that must be considered here. These range from highly malignant sarcomatous neoplasms to benign harmartomatous masses to inflammatory lesions that simulate neoplasms (pseudotumors) (*85–90*). The incidence of specific lesions varies greatly with age. Rhabdomyosarcomas, gliomas of the optic nerve, dermoid cysts, teratomas, metastatic neuroblastoma, chloromas and the "African lymphoma" are seen mainly in the pediatric age group. Lacrimal gland tumors, mucoceles, meningiomas, thyrogenic ophthalmopathy, and metastatic carcinoma are encountered predominantly in adults. Hermangiomas, lymphangiomas, and inflammatory pseudotumors are fairly common in children and adults alike.

A number of noteworthy advances in classification of orbital tumors have been made in recent years. One of the most significant has been the establishment of good histopathologic criteria for separating benign mixed tumors of the lacrimal gland from the malignant epithelial tumors with which they were so frequently confined in the past (*91*). This distinction has permitted conservative surgical management of the former and has indicated the need for radical surgery on the latter.

Another important contribution has been the recognition that some highly malignant sarcomas, especially osteogenic sarcomas, were etiologically related to excessively high doses of X-ray that had been used to control retinoblastomas (*92*). This experience led to a drastic reduction in the amount of radiation used (see earlier section on retinoblastoma).

In the past, rhabdomyosarcoma was considered an extremely rare orbital tumor; today it is widely recognized as being the most common primary malignant neoplasm arising in the orbits of children (*93*). This does not indicate increasing incidence—only better recognition of the tumor. Correct diagnosis here is most important; it indicates the necessity of early radical surgery in an effort to save the child's

life, since this has proved to be one of the most highly lethal tumors with which the ophthalmologist must deal.

Masses of lymphoid tissue developing in the lacrimal gland or elsewhere in the orbit have, in the past, generally been labeled as "lymphosarcoma" or "malignant lymphoma." Now it is becoming apparent that many such lesions are nonneoplastic reactive proliferations of lymphoid tissue of obscure etiology (*94*). The histopathologic distinction between lymphosarcoma and reactive lymphoid hyperplasia is not always easy, and there are still too many cases that the pathologist cannot readily interpret. This is an important area of ongoing research—the clinicopathologic and followup study of lymphoid tumors of the orbit. The distinction is clinically important for therapeutic as well as prognostic reasons. Large doses of X-ray and use of cytotoxic agents should be reserved for the malignant lymphoid tumors.

Endocrine exophthalmos has been the one entity that has been most thoroughly studied, and it continues to be a field of very great clinical and research interest (*95, 96*). With respect to orbital tumors, it has now become widely recognized that a derangement of the hypothalamic-pituitary-thyroid axis is the most common cause of unilateral proptosis (*87*).

The recent studies of Burkitt and colleagues (*97–99*) in Uganda have profound epidemiologic interest. These workers have established that a distinctive form of lymphosarcoma is the most common of all malignant neoplasms in children in equatorial Africa. While the "Burkitt tumor" also occurs in other geographic areas, including the United States (*100, 101*), it is quite rare. This tumor is of ophthalmic interest because it arises in extranodal tissues, with a striking predilection for the bones of the face. Tumors arising in the maxillary and orbital bones are often first recognized because of ocular complications.

Diagnosis

Reese has emphasized the fact that, until a biopsy specimen is obtained, there is no certain way of establishing the nature of an expanding mass in the orbit. There is a great need for more reliable methods of localizing the mass and ascertaining its nature preoperatively. Improvement in soft tissue X-ray techniques, including the use of contrast media; ultrasonography; radioactive scanning techniques; arteriography and venography all need more widespread testing and evaluation (*96, 102*). In his annual reviews of the past 3 years, Dr. I. S. Jones (*96*) provides many references to recent publications dealing with these various adjunctive methods of orbitography.

At the time of exploration, selection of the best approach is of paramount importance. While the intracranial route once enjoyed great popularity, experience has proved it to be very unsatisfactory and actually contraindicated for most lesions. The main exception is the tumor that involves both the cranial cavity and the orbit. The lateral approach to the orbit is preferred by most ophthalmic surgeons who have had considerable experience with orbital tumors (*87, 89, 90, 96*).

Once having exposed the lesion, the question arises as to whether it should be excised or biopsied. If feasible, it is preferable to remove the mass completely, because cutting into a malignant tumor or an infectious granuloma might disseminate the disease. Even rupturing the capsule of a benign mixed tumor of the lacrimal gland tends to seed the wound with a viable tumor. It is possible that freezing techniques may facilitate biopsying a lesion without spreading it into the wound.

Treatment

Since there are so many different types of orbital tumors, it naturally follows that there are many different ways that these lesions must be handled. The highly malignant and infiltrative primary tumors (e.g., rhabdomyosarcoma and malignant epithelial tumors of the lacrimal gland) are usually removed by exenteration of the orbit, together with resection of part of the bony wall of the orbit if deemed necessary. The adjunctive use of preoperative or postoperative radiation and/or cytotoxic agents needs continued study to determine the most effective means of controlling these highly lethal tumors. Many of the benign tumors or very low-grade malignant neoplasms (e.g., hemangiomas, dermoid cysts, teratomas) are, if possible, excised in a more conservative fashion, avoiding damage to the eye and optic nerve. Gliomas of the optic nerve are very low-grade neoplasms, and their proper treatment is a controversial issue. Most ophthalmologists recommend resection of the affected portion of the nerve, but others favor radiation or no therapy. Other lesions (e.g., lymphomas, lymphoid hyperplasias, and metastatic carcinomas) are radiated or treated by cytotoxic agents. Steroids and other medical methods are employed for inflammatory pseudotumors and endocrine ophthalmopathy (*96*).

One of the basic difficulties concerning proper therapy of orbital tumors relates to our ignorance of the etiology and pathogenesis of some of the most important lesions. Endocrine ophthalmopathy, inflammatory pseudotumors, and lymphoid hyperplasia are good examples of rather common benign lesions of obscure etiology and pathogenesis that are generally treated medically by nonspecific methods. Much more work is needed to determine the pathogenesis of these; this in turn should make it possible to improve their therapy. This is an area in which

the interdisciplinary approach at a few large medical centers merits more attention. Orbital tumors are sufficiently infrequent and present such difficult problems in differential diagnosis and management that they are beyond the capabilities of most practitioners. A team of interested and experienced physicians including, in addition to an ophthalmologist, a radiologist, radiotherapist, neurosurgeon, rhinologist, and endocrinologist would be much more likely to cope satisfactorily with manifold problems surrounding orbital tumors.

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EXPERIMENTAL ONCOLOGY

Interest in ocular neoplasia has been almost exclusively clinical, and very few attempts have been made to use the eye for fundamental work. The most noteworthy exceptions are the important contributions of H. S. N. Greene, who developed the technique of implanting heterologous tumors into the anterior chambers of experimental animals (*103*). His experiments demonstrated that, while adults' normal tissues, benign tumors, hyperplasias, precancerous lesions, and inflammatory granulomas were incapable of heterologous transfer, embryonic tissues and certain cancers showing no consistent morphological differences could be divided into two groups on the basis of their heterotransplantability into the guinea pig's anterior chamber. Those human tumors that were transplantable proved to be rapidly fatal, while patients with nontransplantable tumors tended to survive for long periods. Of ophthalmologic interest is the fact that among the 123 tumors, there were only two ocular melanomas. Neither was transplantable, and both patients were alive 7 years later. It would be of considerable interest to study a larger series of ocular tumors by this technique. The ever-increasing recognition that most uveal and conjunctival melanomas, as well as virtually all epibulbar carcinomas, are much less malignant than their counterparts in other tissues suggests inherent biologic differences that might be studied by Greene's method.

It is a curious fact, largely overlooked by general pathologists and oncologists, that of all the tissues of the animal body, the lens is the one that seems to be most immune to cancer. The cells of the lens persist throughout the life of the animal and, therefore, are older than most other cells of the body, which are replaced. This fact, together with the knowledge that mitotic division continues in the lens epithelium for many years, would make one expect the lens to give rise to its fair share of neoplasms. Almost nothing has been done to study this curious situation experimentally. Ida Mann, however, was able to experimentally produce three tumors that she believed had their origin in the lens epithelium of inbred strains of mice (*104*). In each of these three successful experiments, the lens had been transplanted subcutaneously with methylcholanthrene, and the lens capsule had been ruptured. Her experiments suggest that the lens is capable of undergoing neoplastic change, but that the peculiar position of the normal lens, enclosed within the semipermeable capsule and devoid of supporting stroma and blood supply, protects it from various carcinogenic stimuli, even in the experimental animal. Recently, however, von Sallmann and coworkers (*105*) have found that rainbow trout maintained on a thioacetamide diet for prolonged periods develop cataracts. Histopathologic study of the lenses revealed neoplastic transformation of the epithelium, which sometimes replaced a large portion of the anterior cortex.

The most vigorous recent effort to induce neoplastic change in ocular tissues was reported by Patz and coworkers (*106*). Administering methylcholanthrene to mice, they did succeed in producing squamous cell cancers of the cornea, conjunctiva, and epithelial downgrowths into the anterior chamber, as well as adenocarcinomas of the harderian gland and sarcomas of the orbit. They also observed the development of a few uveal neoplasms that they interpreted as amelanotic malignant melanomas.

In the course of a study on the effects of alternate systemic administration of DL-ethionine and N-2-fluorenlyacetamide in inducing tumors in white rats, two animals developed signs of an intraocular neoplasm (*107*). In one case, the eye was studied microscopically and found to contain a huge iris tumor interpreted as an amelanotic spindle A malignant melanoma. The author stated he could find no reports of the spontaneous occurrence of intraocular tumors in white rats (*107*). The technique used in this study might provide the first really good experimental model for the study of uveal melanomas and their treatment. The transplantable melanoma of the Syrian golden hamster has already been used, as noted earlier in this report (*108*).

A study has been made of circulating tumor cells in the eye, using the Brown-Pearce and V–2 carcinomas in domestic rabbits (*109*). When viable neoplastic cells were used, metastatic intraocular tumors were observed almost exclusively in the anterior uvea. (This is in sharp contrast with metastatic carcinomas in man.) Interestingly, when stained tumor cells were injected, the arrested cells and clumps of cells were distributed in random fashion with less involvement of the vessels in the anterior uvea. The predominance of metastatic tumors in the rabbit's anterior uvea, therefore, does not appear to be the result of a greater concentration of arrested tumor cells in that part of the uvea.

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OCULAR TUMORS IN DOMESTIC ANIMALS

The most prevalent and (for economic reasons) most important ocular tumors in domestic animals are the very interesting group of squamous cell tumors of the eyelid and conjunctiva in cattle (*110, 111*). This group of tumors comes closer to providing a suitable experimental model than any other ocular tumor. Some of the remarkable similarities between the bovine and the human epibulbar tumors have already been noted. There is one striking difference, however, with respect to pigmentation. Conjunctival carcinomas in man are observed more frequently in deeply pigmented races, while in the bovine eye, the frequency of such tumors bears a curious inverse relationship to pigmentation (*112*).

Another naturally occurring tumor of cattle and of other species that might prove to be a useful experimental model is the lymphomatosis group. In cattle, these lymphoid tumors exhibit a predilection for the orbit, while in dogs and cats, the globe is often invaded (*113*).

Primary intraocular tumors in animals include uveal melanomas and epithelial tumors arising from both the pigmented and nonpigmented neuroepithelial layers of the nonsensory retina. Uveal melanomas exhibit a similar range of histopathologic and biologic variation in man, but the total number of cases studied is small. The epithelial group of primary intraocular neoplasms seems to be relatively more prevalent in domestic animals than in man.

Retinoblastoma is virtually unknown in the animal eye. This is extremely unfortunate, since it would be extremely interesting to study the genetic aspects of these tumors in domestic animals.

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SUMMARY

Retinoblastoma, the malignant retinal tumor of childhood, once was an almost invariably lethal cancer. Today it is possible to save the child's life in over 90 percent of favorable cases, and as a result of earlier recognition the percentage of such favor-

able cases has been increasing. There are, however, still many difficult problems in differential diagnosis—some leading to a long delay in instituting proper treatment for retinoblastoma, and others leading to unnecessary enucleation of the eye for a simulating nonneoplastic lesion. Development of better clinical and laboratory methods for the early diagnosis of retinoblastoma are needed. Since most of these tumors are still being treated by enucleation, there continues to be a need for the perfection of other therapeutic methods that will permit preservation of the eye and of its function in a larger percentage of cases. Physicians need to become better informed about the genetic aspects of the retinoblastoma problem; they must also obtain the necessary family histories, so as to be better able to properly advise the parents and surviving patients about the chances of the tumor's appearing in other members of the family.

Malignant melanoma of the uvea presents many difficult problems in clinical diagnosis, and much work needs to be done to improve the frequency of correct preoperative diagnosis. In some cases, particularly those treated for retinal detachment and those with opaque media, there is a long delay before the eye is enucleated. In such cases, the chances of the tumor spreading into the orbit or to other parts of the body are greatly increased. On the other hand, 20 percent of the lesions observed clinically and suspected of being uveal melanomas prove to be some other, simulating lesion. Histopathologic and followup studies have revealed malignant melanomas to vary greatly in their degree of malignancy. Some are locally malignant but have little potential for distant spread. Most tumors of the iris are of this type, and they can usually be effectively managed by local excision. In the case of choroidal melanomas, it is currently impossible to ascertain the type of tumor present before enucleation.

One of the most pressing needs is for a better understanding of the natural history of uveal nevi and melanomas. Almost nothing is presently known about the natural course of untreated melanomas, yet the popular belief is that there are highly malignant cancers that must be treated by prompt enucleation if the patient's life is to be saved. Until very recently, only iris tumors were considered suitable for surgical excision; now it has become well established that certain small tumors of the ciliary body can also be excised without seriously affecting the functional state of the eye. Perhaps new cryosurgical techniques will someday make it possible to safely biopsy and/or excise tumors of the choroid.

Tumors of the Eyelid and Conjunctiva.—These tumors are situated externally, where they are usually observed early in their evolution by the patient and his family. Their growth can be easily documented by serial photography, and complete excision usually presents no problem. The main difficulties encountered with these lesions are in histopathologic interpretation, prognostication, and appropriate therapy.

In the past, there has been a great tendency to overdiagnose malignancy and overtreat benign lesions; in recent years, however, pathologists have come to believe that a number of lesions previously considered cancerous are actually noncancerous. Because of this change in histopathologic evaluation, the trend has been toward more conservative surgery for lid and epibulbar lesions. Similarly, lesions previously considered precancerous because they were thought to almost always progress to malignancy are now being treated by wide local excision and/or radiation; the efficacy of these sight-preserving measures is still to be confirmed, however.

Orbital Tumors.—These are hidden lesions. Unlike those of the lids, conjunctiva, and intraocular tissues, they cannot be examined directly except by surgical exploration. Even then, the value of direct examination in differential diagnosis is minimal. Therefore, clinical diagnosis must be based on an adequate body of information, obtained by taking a good history; by use of the results of general physical and ophthalmological examinations; and by use of radiological and other specialized laboratory studies. Usually, however, surgical exploration with biopsy is still necessary before a definitive diagnosis can be made.

In no other category of ocular tumors is the range of diagnostic possibilities so great as in the case of orbital tumors. In all age groups, from birth to old age, one encounters a variety of perfectly benign and highly malignant lesions. Proper treatment obviously depends in part upon correct diagnosis, but even with correct early diagnosis, much remains to be learned. For example, no one is certain how rhabdomyosarcoma, the most frequent primary malignant orbital neoplasm of childhood, is best treated. Most authorities recommend early exenteration, but there are suggestions that excision combined with radiation and/or chemotherapy may be just as successful.

General Recommendations.—The field of ocular oncology is one that boasts few highly trained, broadly experienced investigators. Because of the lack of good experimental models and the rarity of comparable naturally occurring tumors in animals, progress will have to be made mainly in the clinical and laboratory investigation of humans with these tumors. Intraocular and orbital tumors and the lesions that simulate them are sufficiently unusual and of such importance that specialized treatment centers should be developed, to which patients could

be referred for thorough clinical, epidemiological, and laboratory investigation. These centers should, of course, be staffed by highly trained clinical and laboratory investigators, well versed in all the modern techniques of diagnostic ophthalmology—the use of radioactive isotopes, ultrasonography, fluorescein fundus photography, and so on. Experience gained in such centers should reduce the errors made in preoperative and in histopathologic evaluation and should eventually lead to better methods of appropriate treatment, with greater conservation of vision and improvement in mortality statistics. Such centers should also be staffed with experienced epidemiologists and geneticists. Centers of this type should be located not only in the United States but also in selected foreign countries, where environmental and racial differences are associated with interesting differences in the types of tumors encountered. Ideally, such centers should include research facilities and personnel for development of the much needed experimental models of the various ocular tumors of man.

Chapter 18—OCULAR TRAUMA AND TRANSPORT OPHTHALMOLOGY

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INTRODUCTION

This section of the report is concerned with the problems of mechanical trauma to the eyes, and excludes drugs and chemical injuries which are covered in Dr. Grant's paper. As Dr. Hunter Sheldon, Chairman of the American Board of Neurosurgery, has said, "The only treatment for head injury is prevention"; likewise, this report concentrates on factors in protection of the eyes from physical injury rather than on repair techniques.

SCOPE OF THE PROBLEM IN MECHANICAL TRAUMA TO THE EYES

Industry has achieved major results in reducing accidental trauma and lost eyes. Similar prevention is now needed in the areas of nonoccupational, domestic, and transport accidents. Slusher and Keeney in 1965 (*1*), tabulated initiating etiologies in 424 monocularly blind individuals among 21,000 active private patients. When grouped according to decade of life at onset, the first decade (1–10) revealed nearly three times greater frequency distribution than the next most affected decade (age 71–80), and approximately 10 times the frequency found in the most favorable decade (age 21–30). Essentially half of the (160) lost eyes in the first decade of life were due to trauma. Injuries constitute a more frequent and more serious loss of eyes than most ophthalmologists generally acknowledge.

On the other hand, etiologic analysis of blind-school populations reflects binocular lesions of early life; thus, since trauma less frequently blinds both eyes, nontraumatic causes appear to account for a larger percentage of the blind in this blind-school group.

On April 21, 1966, William Dale Anderson of the Walter Reed Hospital, Washington, D.C., reported the cost of lost eyes or enucleations in military personnel during the period from June 1959 to May 1964. His study was based only on eyes or ocular remnants received at the Armed Forces Institute of Pathology and, therefore, represents a minority of eyes lost from military personnel. Within these 5 years, 216 eyes were studied. Eighty-four percent had been lost due to trauma.

The direct costs to the Government for the results of enucleation were calculated on the basis of monthly pensions and life expectancy (private, first class, $100 a month, 50-year life expectancy; sergeant, $140 a month, 40-year life expectancy; major, $300 a month, 35-year life expectancy). The cost for a private, first class thus amounts to $60,000, a sergeant $67,000, a major $125,000. This is aside from: (1) Direct medical service costs, and (2) cost of training the replacement soldiers. A 5-year summation of the costs for the 216 enucleations in the survey was estimated to be $14,657,000.

Twenty-four eyes, or 11 percent of the group, had retained intraocular foreign bodies, nine of which would have presented salvage possibilities had better localization techniques such as ultrasound or more critical Roentgen diagnosis been used initially. With protective lenses or goggles, 19 eyes would have been saved, another 19 *probably* saved, and an additional 73 *possibly* saved. Many of the involved individuals did wear spectacles, but no data were available as to whether safety lenses were used and whether spectacle lens fragments themselves compounded the injury. Captain Anderson, however, repeated the plea voiced by Dr. John R. Fair of Atlanta (2) for safety eye armour to be worn by combat personnel and for all service-prescribed spectacles to be made from safety lens materials.

PROBLEM AREAS IN REDUCTION OF OCULAR TRAUMA

Development of Improved Impact-Resistant Glass Products

The development of thermally toughened glass dates from the 1870's, when François de La Bastie of

Paris developed an oil-immersion hardening process for glass. The first U.S. patent in this field was issued to de La Bastie in 1874. Significant ophthalmic use, however, did not evolve until 1912. Aside from process refinement, no fundamental advances appeared in this field until the Corning Glass Works (Corning, N.Y.) evolved their "Chemcor" process with exotic barium lithium glasses which are chemically treated in molten lithium after final surfacing. Chemcor has unique properties of flexibility and great impact resistance in lenses much thinner than required by current Federal goggle specifications. The optical qualities of Chemcor are quite uniform and satisfactory,[1] but the compression layer or outer skin is thin, measuring approximately 100mμ to 200mμ whereas the compression layer in heat treated and chilled (thermally toughened) glass may measure 0.7 to 0.8 mm. in thickness. Very superficial scratches or mars therefore can ventilate the stress-strain system in Chemcor lenses, whereas much deeper surface faults are required to impair the impact resistance of conventionally treated crown glass lenses. Pilot marketing evaluation of these Corning lenses, undertaken in 1965 by several major ophthalmic lens distributors, has been interrupted. Thin lenses in truly protective glass would increase user acceptance and wider dissemination of protection because of reduced lens weight and less conspicuous appearance.

Further research is needed in the development of thin cosmetically acceptable protective lenses of high-impact resistance (*3*).

Development of Improved Impact-Resistant Plastics for Lenses and Glazing

The transparent organic plastics (American Society for Testing Materials, Class 1 Plastics) have high-potential value both as good optical lenses and mechanical shields on the basis of excellent resistance to low- and high-velocity impacts, marked resilience, optical stability, and refractive indices (1.41 to 1.68) only slightly below those of ophthalmic glass.

Experiences from 1935 with methyl methacrylate (Plexiglass, Lucite, Polymer K, Perspec, Transpex, etc.) indicated fairly stable optical properties but poor surface hardness. The latter makes these acrylics, like polystyrenes and cellulose acetate, unsuitable for spectacle wear. A mechanical advance was achieved in 1942 with the introduction of allyl diglycol carbonate resins for ophthalmic lenses. This was produced by the Columbia Southern Corp. of Barbertown, Ohio (a subsidiary of Pittsburgh Plate Glass Co.), under the trade name CR–39. This material (allyl resin) shows very little tendency to yellow over years, and its surface hardness or scratch resistance is significantly better than methyl methacrylates. It is distressing to realize that no fundamenal improvement in optical plastics has been achieved since the introduction of CR–39. A problem in the American plastics industry is that tonnage requirements for such optical plastics are low and therefore little profit can be envisioned in the refinement of this material for lens use. Unfortunately, the introduction of a new French plastic lens (Telor Orma 1000, La Lunette de Paris, Inc., 1961) proved again to be a recurrence of the basic allyl resin, CR–39 (*4*). Military stimulus, however, has maintained some research in optical plastics under the aegis of Personnel Armour Materials Research Section, Clothing and Organic Materials Division, U.S. Army Material Command, Natick Laboratories, Natick, Mass (*5*).

In 1966, however, 24 years after the introduction of CR–39, the principal material of study in this report is CR–39 with lesser information concerning polyvinylbutyral. The Natick Laboratories report sophisticated studies by color photography at 26,000 frames per second in analysis of the birefringence stress-strain patterns occurring in such plastics under high-velocity (rapid loading) impacts.

Much more fundamental work is needed in the development of better optical plastics and better evaluation of their mechanical characteristics.

Development of Phototropic Lenses for Graduated Protection Against Radiant Energy

Lenses which change optical density in response to changes in illumination have intrigued ophthalmologists since World War II. Though phototropy has been recognized by chemists since 1881, little work was done on the application of this principle to protective lenses until the past decade. Triphenylmethane dyes are phototropic, but their reactions are generally slow and achieved optical densities are not high. Similiarly, electromechanical goggles with explosive dimple motors have been designed for rapid protection against radiation of nuclear explosion. Although adequate reaction speed is achieved with these devices, they are cumbersome and require several ounces of headgear and body-attached equipment. Electrochemical processes, such as high-speed electroplating, have also been studied but seem to be slower than the electromechanical goggles.

The Pittsburg Plate Glass Co. has sponsored studies at the Mellon Institute with optical pumping compounds such as cerium or europium in dilutions of 100 parts per million incorporated in initial glass melts. These produce an amethyst or purplish density upon exposure to bright sunlight and will reduce transmittance up to 40 percent. Under laboratory conditions, greater densities have been reported.

[1] Index of refraction 1.523; Littleton softening point 670°C.; Annealing point 510°C.

More recently, Armstrong and Stookey have produced photochromic silver halides which can be added to conventional silicate glass, producing color reversibility. Darkening extends slowly over a period of an hour and is accelerated by low temperatures (reverse thermal coefficient). Fading is more rapid. There is essentially no fatigue to these reactions, but they are by no means rapid enough to protect against nuclear explosion or even the demands of highway driving in and out of tunnels. Darkening is largely a surface phenomenon involving only a few tenths of a millimeter; thus, a type of uniform density is achieved regardless of variations in thickness. Lenses of this type are produced by Corning Glass Works under the name "Eye Comfort."

Coated organic plastic lenses (photochromic) have been under study by the Chemical Experimental Division of NCR and have been produced by many companies under the name "Rayex." Similar photochromic coatings are produced by the American Cyanamid Co., but again, reactions are slow and easily fatigued. Nuclear Research Associates of Long Island City, N.Y., have also been working in this field but do not as yet have a marketable product.

Research yielding rapidly phototropic materials largely unaffected by temperatures which the body can endure would be invaluable in protecting the retina from burns of accidental or hostile nuclear explosions. They would also enhance mesopic or driving vision at the end of a day by graduated protection of retinal sensitivity from bright daytime intensities as those encountered on beaches or in the snow.

Management of Ocular Trauma When Prevention Has Failed

The salvage of eyes injured mechanically depends primarily on the initial extent of laceration and disorganization. Loss of injured eyes from secondary infection has been largely eliminated since the advent of sulfa drugs in the late 1930's and the systemic antibiotics in the early 1940's. Visual salvage following lesser wounds has been significantly improved by the development of finer and more precisely ground surgical needles as well as the advent of suture materials smaller than 6–0 (*6*).

There is pressing clinical need, however, for development of microsurgical equipment (operating miscroscopes and correlated instruments) which is simple, compact, easily maintained, and economically procured (*7*). Simplicity and practicality in such instruments would greatly enhance widespread use, produce more accurate repair of anterior wounds, and reduce surgical trauma in removal of foreign material. Added specificity is also needed in most clinical training centers where ophthalmic surgeons are developed (*8*). Similiar emphasis needs to be directed toward the functional design and architectural planning of optimal ophthalmic operating rooms with easy admission of refined equipment (operating microscopes; ultrasound; Berman localizers; magnets and metamagnets) to the area of the patient's head (*9*). Very little in ingenious design has been offered to the eye-operating environment.

TRANSPORT OPHTHALMOLOGY

The Driving Task and Qualifications for It

Studies in the ophthalmology of driving has been subject to theoretical limitation and biostatistical criticism because the driving task has not been clearly defined and criteria for satisfactory accomplishment not established. Accident-free driving records are inadequate to assess safe driving or driver ability. Accident-exposure factors and mileage driven are seldom quantitated in accident data.

Definition of the task and validation of criteria for proper accomplishment should be established, thus reducing bioengineering and biostatistical objections to most medical studies in the field. Meanwhile, traditional principles of clinical judgment as applied to other medical problems have been exercised in creating provisional definitions and criteria. As it is difficult to substantiate a cutoff point for visual limitation in vehicle operation, it is similarly difficult to defend cutoff levels in other physical impairments. It is obviously necessary for a driver to have structural appendages enabling him to reach controls of the vehicle, yet it is uncertain how much neuromuscular ability or structural flexibility is demanded for vehicle operation. Highly specific criteria sometimes lead to absurdities, such as in one State where ankylosing spondylitis of the cervical vertebrae precludes driving if the applicant can rotate his head on his shoulders only 34°, but permits him to drive if rotation of 35° is possible. Other data from the Indiana State Police indicate that, among accident surviving drivers, those having better vision were involved in more severe accidents whereas those with less good vision were involved in less severe accidents. If extrapolated to the ridiculous, this would suggest that a blind driver would be the safest driver (*10*).

Current statistics must be interpreted in a practical sense based on the desire for optimal biological function in every capacity. Driver limitation may be created by major impairments in a single capacity (e.g., vision) or by minor impairments in several capacities (e.g., slight loss of visual field combined with slight limitation of head rotation due to ankylosing spondylitis) (*11*).

Color Vision

Color vision defects have never been proved to contribute to transport accidents (*12*). This aspect of traffic control can be largely engineered out of significance by admixing other hues with red and with green. Also, it has long been recommended (*13*) that red or stop signals should be designed in bar configuration to indicate a bar to progress, whereas green signals should be in the conventional round form.

Aging

The role of chronologic aging is well documented in its interference with accommodation, mesopic vision, and other biological factors in driving (*14*). However, the extensive effect of almost any ocular pathology on mesopic vision has not been well correlated with most eye impairments and is not appreciated by most ophthalmologists.

There is also pressing need for rapid testing procedures and equipment to be operated by lay individuals which will yield reliable data on photopic corrected central acuity under conditions of movement (*15*), horizontal form fields, and mesopic factors of vison (acuity in reduced illumination, glare tolerance, and glare recovery time) (*16*).

Much of the literature is scattered in nonmedical publications, and a major amount is contributed by psychologists. Often this is not correlated with medical, and more particularly, with ophthalmological work. Unfortunately, in many of these studies, there is a tendency to overlook some basic medical variable in the experimental design.

"Research on Human Variables in Safe Motor Vehicle Operation" (George Washington University, June 1961) by L. G. Goldstein, analyzes 111 papers covering 270 prediction variables. Many of the studies gathered in this document prove not to have statistical validity.

Many conferences of potentially widespread importance have yielded pleasant interchange between individuals responsible for large programs but do not seem to have produced specific data, new research, or applied results (cf. approximately 40 meetings of the Committee on Trauma of the National Academy of Sciences, National Research Council, Division of Medical Sciences; also Armed Forces, NRC Committee on Vision, symposium on Visual Factors in Automobile Driving). Since 1954, the President's Committee for Traffic Safety (an outgrowth of the President's Highway Safety Conferences dating from 1946) has been under a 40-member Advisory Council; in 1962, the Council established a new section of their "Action Program" to be concerned specifically with health, medical care, and transportation of the injured.

A uniquely large volume of crash investigation statistics has been derived since 1952 by the Automotive Crash Injury Research (ACIR) program at Cornell. Morbidity and mortality data from the U.S. Army during the Korean conflict pointed out that more men were lost from auto accidents than combat. Under Army request, Cornell Medical College in New York City directed a major segment of their Crash Injury Research to the automobile field. ACIR Bulletin No. 4 (March 1963) analyzed 28,000 rural injury-producing accidents in cars carrying 62,000 occupants, 75 percent of whom were injured. Ocular and orbital injuries occurred in nearly 10 percent of the injured occupants and were twice as frequent among front seat as rear seat occupants. Seventy of these were "serious" injuries, with avulsion or enucleation involving one eye in 29 persons. Severe lacerations comprised 15 percent of all oculo-orbital injuries. When ocular injury occurred, there was loss or major impairment of vision in about 40 percent. Other studies from Cornell, however, have been disappointingly less specific (cf. study of automobile glazing as an injury factor in accidents, March 1966) and have generally avoided pinpointing specific manufacturers' products in relation to injury production. In 1958, responsibility for ACIR was transferred from the Medical College to Ithaca, N.Y., and in 1962 the project was moved to the Cornell Aeronautical Laboratory at Buffalo, N.Y.

A resumption of closer medical supervision, direction, and liaison might strengthen the yield from much support extended by the USPHS Division of Accident Prevention, by the Automotive Manufacturers Association, and by the six-member Advisory Board to the General Services Administration to recommend Federal standards for vehicles.

In general, ophthalmic clinicians are not attuned to the significance or extent of visual factors in transportation, and ophthalmic research workers have bypassed their exploration. Research projects have been actively solicited by the USPHS Division of Accident Prevention, but pressing clinical demands have prevented the participation of most ophthalmic workers. The rosters of contributors in transport vision or concerned local and national bodies are remarkably devoid of ophthalmologists or physicians of any discipline. Medical orientation in accident causation and injury prevention would add a needed substantial dimension toward the reduction of mounting deaths and injuries on our roads.

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Chapter 19—TRAUMA TO THE EYE FROM TOXIC AGENTS

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INTRODUCTION

Eye trauma from toxic agents includes injuries from external contact with chemicals, toxic effects from foreign bodies which have penetrated into the eye, and disturbances of the eye and impairment of vision from systemic poisoning by chemicals and drugs.

SOURCES OF INFORMATION

Sources of information on eye trauma from toxic agents consist of numerous original reports scattered in the periodical literature on ophthalmology, industrial medicine, general medicine, and neurology. Reviews of pharmacology and toxicology published in the "AMA Archives of Ophthalmology" have a valuable function in organizing most of this material annually. Otherwise, references to original works must be sought through indexing or abstracting systems such as the "Index Medicus," "Chemical Abstracts," "Excerpta Medica" (Ophthalmology), and the "Zentralblatt f.d. ges. Ophthalmologie."

There are few recent books on the subject. The only books devoted to it in English are "Toxicology of the Eye" by W. M. Grant (1962) (*1*) and "Occupational Eye Diseases and Injuries" by J. Minton (1949); in French, there is "L'oeil et les maladies professionnelles" by C. Coutela (1939) and in German, "Augenschadigungen in Industrie und Gewerbe" by P. A. Jaensch (1958).

Additional collections of relevant material are found as chapters, or disseminated through the text in "Textbook of Ophthalmology" (vol. VI) by S. Duke-Elder (1954), "Systemic Ophthalmology" edited by A. Sorsby (1958), and "Clinical Neuro-Ophthalmology" by F. B. Walsh (1957) (*2*).

At least one file catalog is maintained on all published material on the subject. This is at the Massachusetts Eye and Ear Infirmary in the Howe Laboratory of Ophthalmology. It has not been possible to include in this file, data accumulated by commercial organizations from their own testing, or by the American Medical Association's Registry on Adverse Reactions based on case reports from physicians, except when this material has been made publicly accessible in print.

TYPES OF EYE INJURIES

Chemical burns of the eye are commonly caused by splashes of acids, alkalies, other corrosive chemicals, and certain solvents. Less commonly, damage results from exposure to injurious gases or vapors. Chemical burns of the eye are a problem not only in the many industries and trades where dangerous chemicals are handled, but also in homes and schools. In chemical manufacture, there is great variety of dangerous material, but the dangers are reduced by considerable attention to prevention and prompt first aid. In certain trades and occupations outside of organized industry, chemical injury of the eye is an occupational hazard—for instance, plasterers and masons are subject to lime burns, and tunnel excavators are subject to painful injury of the cornea from the hydrogen sulfide released by rotting organic matter. The garage worker is subject to burns by battery acid and to severe discomfort from brake fluid splashed in the eye. In the home, lye, ammonia, and strong detergents cause most accidental burns of the eye, but many other substances ranging from perfume to cement are occasionally involved. In school, splashes of alkalies and acids and laboratory explosions cause some serious eye damage. In certain areas, severe eye injuries are produced by the criminal practice of throwing caustic into the eyes.

Damage from splashes of chemicals or exposure of eyes to poisonous gases and vapors generally is limited to the most directly accessible anterior portions of the eye—the cornea, conjunctiva, and sclera. The caustic action penetrates to involve the iris and lens only in the most severe injuries.

In the worst types of burns, produced by splashes of concentrated strong acids and alkalies, the tissues of the anterior part of the eye actually disintegrate, and the remainder of the eye is left useless. In less severe burns, the most important effect is opacification of the cornea, which reduces vision and may

cause blindness. In milder burns, such as those produced by splashes of various neutral solvents, the injury usually is superficial, and, though temporarily painful and disabling, is capable of complete healing. Many gases and vapors, including smog, produce stinging and burning sensations in the eyes without actual visible injury.

Metallic foreign bodies that penetrate into the eye in accidents are a potentially serious source of toxic eye trauma, particularly when iron, steel, copper, or brass is involved. These metals gradually react within the eye and can disastrously poison and destroy it.

Systemic poisonings by chemicals and drugs occasionally cause disturbances of the outer portions of the eye, but more commonly injure the deeper portions.

Cataracts are the most serious consequence of toxic effects on the lens of the eye. Less serious effects are discolorations and disturbances of the focusing power of the lens. These effects are serious to the patient insofar as they interfere with his vision; at worst, they may necessitate cataract surgery.

Poisoning of the retina and optic nerve is generally the most serious of all the internal toxic effects on the eye, since this may cause partial or complete loss of vision, which may be permanent. The best known poisons, responsible in hundreds and probably thousands of such cases, are methyl alcohol and quinine. Oxygen has caused many cases of blindness by inducing retrolental fibroplasia when used to excess in treatment of newborn babies (*3*), and precautions must be taken not to disturb vision by excessive concentration and pressures of oxygen in the atmosphere of divers or flyers (*4*).

Poisons affecting the brain occasionally indirectly disturb the eye and reduce vision. Movements of the eye required to look in various directions can be upset by carbon monoxide, lead, and barbiturates. Vision can be seriously reduced by damage to the visual cortex of the brain as a consequence of oxygen deprivation and poisoning by carbon monoxide.

INCIDENCE AND VISUAL MORBIDITY

Even without statistics, it can be said that chemical burns of the eye present a serious hazard in industry, in the home, in the laboratory, and sometimes as a criminal device. Though most chemical burns are only temporarily disabling, every year they cause total loss of vision in many cases.

Loss of vision from toxic intraocular foreign bodies of iron or copper is less common, but each year a substantial number of eyes are lost either from the toxic effects, or more commonly from surgery performed in desperate efforts to prevent the toxic effects.

The incidence of toxic trauma to the eye from accidental chemical burns and from intraocular foreign bodies is being reduced by education and safety precautions, but the list of substances and the number of cases involving ocular damage from systemically absorbed toxic agents is at the same time growing. The greatest increase is in adverse side effects of drugs affecting the eye. These side effects have been considered by the Food and Drug Administration to be sufficient cause for prohibiting the use of certain drugs—for instance, triparanol (MER-29), because of development of cataracts in people under treatment for atherosclerosis (*5*), and dimethyl sulfoxide (DMSO), because of changes found in the lenses of experimental animals (*6*), even though no increase in incidence of cataract was reported in patients.

Adverse effects on the eyes are frequent enough to have become the prime hazard and limiting factor in the use of certain drugs which have proved otherwise too valuable to ban. For instance, the risk of inducing cataract in patients under prolonged treatment with drugs related to cortisone has been widely recognized, yet the arthritis or other disease being treated often is severe enough to justify the risk until some treatment entailing less hazard can be found. Similarly, a great many arthritis and lupus erythematosis (*7*) sufferers are faced with a problem in the use of chloroquine and related drugs, and many thousands of mental patients must continue to take phenothiazine derivatives, although both types of drugs may injure the retina and impair vision (*8*).

Somewhat peripheral to the problem of direct injury to the eye by toxic chemicals or drugs is the possibility of harm from glaucoma which might be induced or aggravated by a wide variety of drugs, especially those with atropinelike side effects. That this complication is a common consideration is suggested by the fact that nearly half the drugs advertised recently in the "Journal of the American Medical Association" included precautionary advice regarding glaucoma. (Most of these warnings have been made at the behest of the Food and Drug Administration on purely presumptive grounds, without actual test or proof.) To determine the true incidence of this complication, more clinical investigation is needed.

TREATMENTS

In very few instances is treatment for toxic eye trauma a specific or logical scientific outcome of accurate knowledge of the mechanism of toxic action. With rare exceptions, chemical burns of the eye are treated indiscriminately, first by irrigation to remove residual noxious material, then by gen-

eral measures to allay irritation and inflammation. However, in many cases this simple type of treatment does not prevent serious, permanent damage. As a consequence, a great variety of additional forms of treatment have been instituted. Unfortunately, nearly all of these treatments have been devised on no basis other than speculation or conjecture, and few have been evaluated in any properly controlled, objective manner. A great deal remains to be done in devising effective, specific means of early treatment and in properly evaluating the multitude of different treatments now in use all over the world.

Later management of eyes that have been left scarred by chemical burns is usually surgical, sometimes involving corneal transplantation. This phase of treatment, though presenting extremely complex and difficult problems and though often unsuccessful, has a more sound and logical basis than many of the early treatments. In the repair of scarred and abnormally vascularized eye tissue, serious difficulties deserving a great deal of study and research effort remain to be overcome.

In the case of toxic intraocular foreign bodies such as iron and copper, treatment depends almost entirely upon surgical removal of the foreign body, although in many instances the surgery itself greatly endangers the eye; it would often be preferable to allow a foreign body to remain undisturbed if there were some safe and effective way to prevent or counteract the toxic effects. Numerous substances that have detoxifying actions on iron and copper are under investigation. Some have proven effective in treatment of generalized poisoning by toxic metals in the circulation, but no effective solution to the problem in the eye has yet been found. This certainly deserves continuing and intensified experimental and clinical research.

In cases of derangement of vision by systemically absorbed chemicals or drugs, treatment is, with rare exceptions, not specific for the poison, but depends mainly upon stopping exposure and attempting to rid the body of residual toxic agent. In practically no instance is there sufficiently precise knowledge of the mechanisms of toxic action to permit logical development of highly specific antidotes. However, one type of eye poisoning is the outstanding exception in this regard. It provides a brilliant example of how one mechanism of poisoning has been defined in terms of the enzymes and the specific molecular structures involved, and how this precise knowledge of the mechanism has led to a logical development of effective antidotes to counteract the specific enzyme inhibition and to restore normal function in the eye. The example is the inhibition of cholinesterase by compounds in the category of so-called nerve gases, and subsequent complete restoration of the enzyme activity by nonpoisonous antidotes, such as pralidoxime, which have been chemically designed specifically for this purpose (*9*). The eye disturbance in this particular example happens not to be a serious one—it consists of constriction of the pupil and spasm of the focus of the eye so that all distant objects are seen as a blur—but this example demonstrates what can be achieved by sufficient research directed at the fundamental aspects of a poisoning.

While lack of knowledge of these aspects has prevented development of specific treatments for most other toxic disturbances of eye and vision, benefit has been obtained in the case of optic nerve disturbances by organic arsenic and by inorganic lead through application of the general principles of chelating agents to remove these poisons (by dimercaprol and calcium edetate, respectively). Also, in the case of injury of the optic nerve and retina by poisoning with methyl alcohol, which often leads to blindness, research has given valuable clues to improving treatment through administration of buffers to correct acidosis and administration of ethyl alcohol to interfere with the metabolism of methyl alcohol (*10*). Although the most fundamental details of the mechanism of poisoning by methyl alcohol have not yet been elucidated, what has been learned through research has already sufficed to save the sight, and even the lives, of many patients. If all the details of the mechanism were discovered, we could well expect to be able to devise more specific and more effective treatment.

METHODS OF STUDY

Studies of eye trauma from toxic agents vary according to the nature of the toxic agent—whether it is an external injurious substance, an intraocular foreign body, a poisonous chemical acting systemically, or a drug having adverse side effects on the eye. The purposes of studies on these substances also vary.

Some studies are aimed at detecting or evaluating toxic ocular effects of new chemicals and drugs before they have the opportunity to develop into serious clinical problems; these might be considered preventive studies. Other investigations are aimed at elucidating the fundamental biochemical and physiological mechanisms involved, with the ultimate goal of developing logical and suitable counteraction or treatment against the toxic process. Still other work involves experimental testing, comparing, and evaluating various means of treatment.

Studies concerning chemical burns of the eye from external contact include experimental appraisal of the injurious potentialities of new chemicals, investigation of the biochemical and pathologic mechanisms involved in tissue damage, and evaluation of

methods of treatment. These all depend mainly upon laboratory investigations using experimental animals.

Poisons which may injure the eye after systemic absorption, and drugs which potentially have adverse side effects on the eye, are sometimes identified by routine testing in laboratory animals, but it is not uncommon that testing in both subprimates and monkeys fails to produce effects closely similar to those that occur in human beings. On the other hand, many toxic effects which have been induced in the eyes of lower experimental animals have never been seen in the human eye.

A great many studies have been carried out with chemicals and drugs that cause specific changes in the eyes of lower animals, though not necessarily in those of human beings. These substances are utilized as tools in the study of the enzymes, the metabolism, and the fundamental biochemical and physiological processes upon which the eye depends. Such studies have had great value in these fundamental respects, though they seldom contribute much to solving problems of eye trauma from toxic agents in human beings.

Toxic effects on the human eye usually occur as a result of accidental poisoning, or as an unexpected side effect of drugs used in treating diseases having no ocular implications. In most cases, these effects have been recognized through astute clinical observation and study. Once a connection between a chemical or drug and an ocular disturbance is suspected, efforts are usually made to test the validity of the suspected relationship by determining the incidence of the disturbance in a series of patients who have been exposed to the potential poison, and by comparing the incidence in other series of patients of similar age, sex, and so on who have not been exposed.

Further efforts at substantiating or confirming the suspected relationship usually involve administering the substance in question to animals of various species, on the chance that some may be affected in the same way that human beings are. If this proves to be so, it offers presumptive support for the clinical suspicion—and, potentially more important, the possibility of reproducing the toxic effect in an experimental animal opens the door to investigation of the fundamental biochemical and physiological mechanisms involved. This, in turn, permits development and testing of possible antidotes and also provides an opportunity for testing related chemicals and drugs for similar toxic effects.

Study of the effectiveness of treatments for eye injuries from toxic agents is greatly facilitated when the injury can be reproduced uniformly in animals' eyes, since this permits accurate comparisons of results in untreated and treated eyes, as well as comparisons of different treatments. Evaluation of the effectiveness of treatment in human beings is much more difficult, since the injuries are likely to vary from patient to patient, and comparison of results with and without treatment is generally not feasible.

CURRENT AND RECENT RESEARCH

Search through the "Research Grants Index" (Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health) shows in 1964 only about a dozen research projects concerned in some way with toxic trauma to the eye. Half of these have been devoted directly to the subject, but only to very small areas. The projects most directly applied have been concerned with toxic effects on the retina from phenothiazine drugs, from chloroquine, and from iron. The less directly applied, but potentially contributory projects have been concerned with corneal vascularization, corneal transplantation, experimental induction of diabetes and cataracts, and the adverse side effects of chloramphenicol on vision in the treatment of cystic fibrosis.

This leaves very large areas with *no* NIH-supported investigational activity (as of 1964).

UNSOLVED PROBLEMS

The most fundamental problem is lack of knowledge of basic details of how each chemical or drug injures the eye, either from without or from within. We do not know, but we need to know, how the molecular structure and chemical and physical nature of each substance determine its injurious properties. Likewise, we need to how how injurious substances react with the tissues and precisely how the functions of the tissues become deranged. Problems of predicting toxic properties, devising more effective treatments, and designing more desirable drugs, which are problems of great and present practical importance, presumably would yield much more readily to solution if the first problem were solved.

Elucidating the most fundamental aspects of toxic eye injuries presumably will take a very long time. In the meantime, we have an immediate, practical, and unsolved problem in obtaining adequate, simple, descriptive, but clinically valuable information on the toxic effects of many chemicals and drugs on the eye. Also, we have the practical, pressing, unanswered question of the relative clinical merits of the great variety of treatments which are in use in various parts of the world. What is the best treatment now available?

RESEARCH NEEDS

There is need for much more research than is going on now. Research is needed at all levels, from

the fundamental molecular level to the applied clinical, and on all aspects, from chemical burns to systemic poisoning.

In relation to chemical burns of the eye, probably ample testing of substances for irritative or caustic effects on the eyes is being carried on by chemical manufacturers and others, but the results need to be made more publicly accessible. They should be reported in appropriate journals rather than being stored away in private files. There is much greater need for expansion of research on the chemical and biological changes which occur in the cornea and adjacent tissues when they are subjected to the action of injurious chemicals. This necessitates frontier research in protein and mucopolysaccharide chemistry and tissue physiology. With adequate knowledge of these mechanisms, one could more logically devise treatment to counteract the damage. Many years of study presumably would be required to reach this goal.

More immediately, there is great need for evaluation of the multitude of chemical burn treatments now in clinical use in various parts of the world. This can be accomplished under properly controlled conditions, using experimental animals. It would be of great practical clinical value and it can be done definitively without waiting for further fundamental developments in chemistry or biology. It requires only interested and properly trained people, suitable facilities, and support. To most closely duplicate human eye conditions, monkeys would presumably be the most suitable experimental animals.

Research on ocular disturbance from systemic poisoning or from adverse side effects of drugs needs to be promoted in at least two directions. More diligent clinical research and study is needed for better recognition and evaluation of the many different types of visual disturbances from these sources. This could surely and obviously be accomplished by devotion of more time and interest to systematic study of the problem by adequately trained clinicians. The other aspect of the problem, that of elucidating the mechanisms by which the toxic effects are produced and developing logical countermeasures or treatments for them, is far more difficult, and it merits still greater increase in effort and support.

Research on the mechanisms by which systemically absorbed substances adversely affect the eye or disturb vision requires specially trained investigators and involves scientific methods of great variety and complexity, but precise elucidation of such mechanisms holds enormous potential value in several respects. A complete understanding of a mechanism of poisoning would almost surely carry with it a significant increase in knowledge of the normal processes which were disturbed. Elucidation of the mechanism of a toxic effect offers the best basis for development of a logical treatment or antidote for the disturbance. Recognition of such a mechanism and its relationship to the chemical nature of the agent responsible could provide a rational basis for predicting toxic properties in related compounds and for designing drug molecules with reduced toxicity to the eye.

To come as close as possible to duplicating human eye conditions, investigation of mechanisms of toxic action must depend largely upon work with monkeys, but even the monkey differs too much from the human to provide conclusive findings. This presents a difficult problem, necessitating development of new methods which can be employed clinically to help in determining what is happening in the human eye.

There is a real need for clinical testing which is not being met at present. In fact, the needed testing is becoming increasingly difficult to carry out as the policies of both NIH and FDA oppose studies involving risks to patients. A more realistic facing of the risk problem is needed. For instance, the many drugs which are suspected of being hazardous in connection with glaucoma need to be tested under carefully supervised conditions in order to evaluate this hazard. Because of species differences, this testing needs to be carried out on human beings. The results obtained would be of considerable value to all patients who might find it necessary to use these drugs. In particular, glaucoma patients would stand to benefit from the knowledge gained. Still, for the individual taking part in the testing, there could be risk without personal benefit. This problem could be faced by suitably remunerating or indemnifying subjects willing to run risks for the benefit of others.

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research in rehabilitation of the blind and the partially sighted

part III

Chapter 20—REHABILITATION OF THE VISUALLY IMPAIRED

The Blind We Have With Us

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INTRODUCTION

Part of the purpose of this chapter is to examine the programs and prospects for rehabilitating all those who have suffered substantial visual impairment, whether from illness or accident. The examination of programs calls for a brief if wide-ranging overview, while the prospects take us directly to the area of needed research.

SOME DEFINITIONS AND THEIR CONSEQUENCES

The "substantial visual impairment" which the chapter treats must not be thought of as limited to total blindness or even to so-called "legal blindness." Beyond the numbers who fall into these categories is a far larger number whose visual impairment seriously interferes with the full living available to those with normal vision. Educators, rehabilitation personnel, and others working with blind persons have long used different terms to describe various groups of the visually impaired. Not always clearly defined, certainly not always with a common definition, these terms have included "educationally blind" and "industrially blind"; but the educationally blind have often achieved the highest honors in graduate and postgraduate studies and gone on to full lives in academic or other fields, and many of the industrially blind have proved that they can take a constructive place in industry at any level. In our day, one might be inclined to add an important term such as "automotively blind" to refer to those who could not, or at least should not, take the wheel of an automobile. Unfortunately, if such a term were to be coined, no one could define it. For there is no agreement among the specialists in optics or ophthalmology, let alone among those in charge of the licensing of motorists in our 50 States.

Perhaps it would seem easy to begin with the definition of total blindness, but even here we find a strange disagreement. Some of us would limit this to the absolute absence of sight, but at least one Government agency has held a definition of total blindness as "5/200 or less," and at least some of the persons considered totally blind by workers for the blind have light perception, light projection, or even more. This is not to say that light perception or light projection can be compared with normal vision; it is to say that they are something more than and different from total blindness.

"Legal blindness" (with very slight differences in its wording in some States) uses the criteria both of central visual acuity and breadth of field. Thus it includes both those whose central visual acuity in the better eye with correction is 20/200 or less for distance, and also the group whose central visual acuity might be greater but whose field of vision subtends an angle of 20° or less. There is universal agreement that everyone within this definition has a truly severe visual impairment. Yet the grouping comprehends not a single disability, or two categories of disability, but many degrees of visual impairment. Thus no one can say that the same blindness problem exists for the individual absolutely unable to recognize light, the person with 5/200 vision and a relatively full field, and the person with a serious field restriction but with excellent distance acuity. With proper understanding, the first groups may both be rehabilitated together, making certain distinctions as to the type of rehabilitation and the emphasis given. At the Kansas Rehabilitation Center for the Blind in Topeka, the late Louis Cholden, M.D., one of the few psychiatrists to interest himself in the field of blindness, discovered what others had long suspected—the deep difference between the totally blind and the partially sighted, and the underlying "hostility" (in the psychiatric sense) between them, despite their friendliness and sharing of a common bond.

LOW VISION AIDS

Both within the definition of legal blindness and outside it is a group which can be helped to more effective use of their low vision through optical aids

often spoken of as "low-vision aids" and through training in their use. Many of these aids are of value in reading, enabling the person who could not otherwise do so to read regular print. Some of them are useful in distance work, including "mobility" (the ability to walk from place to place with relative ease, grace, and safety). Two Government agencies deserve credit for stimulating low-vision centers, developing these aids, and making them available to many of the people who can be helped by them. The NINDB has assisted in research in this area, and the Vocational Rehabilitation Administration has also played an important role in these efforts. The latter agency gave the clinics an enormous forward thrust by its selected demonstration grants supporting the establishment of numerous such clinics and bringing to them partially sighted persons who could benefit. What appears to be needed now is a major increase in funding which would allow Government agencies to establish more such centers, train more personnel, and purchase for partially sighted persons those aids which are essential to their well-being. It is already clear that this type of activity can make many persons self-supporting; it is perhaps more important to note that for others, including many older persons, it can make life more livable.

"CONGENITAL" OR "ADVENTITIOUS"

Those suffering substantial visual impairment include both those congenitally so and those whose impairment is adventitious. To the reader unacquainted with the field it would seem easy to make a distinction between congenital blindness and adventitious blindness. Actually it is one of the most difficult distinctions to make. The multiple variables noted in our discussion of the definition of legal blindness are themselves sufficient to make the congenital-adventitious distinction difficult. For example who is to say that the child born with serious visual impairment who loses further sight in early school years, becomes legally blind in his teens, and totally blind later in life is congenitally blind? At the risk of pushing the distinction too far, let us use the Oxford University Dictionary's definition of "congenital": "existing or dating from one's birth, born with one." Is the child born prematurely and blinded by retrolental fibroplasia from the use of oxygen in the incubator congenitally blind?

Lest all this appear to be merely academic, it is important to underline some of the real differences between the congenitally and the adventitiously blind. For the moment, we confine our discussion to those who are totally without sight. If this utter lack of vision has existed from the moment of birth, training for life can at no time call on visual memories; one must presume a totally different mode of achieving knowledge; one must expect a differentiation at least in the visual cortex; and there must exist or be developed specific methods of educating and training. As yet no one is able to tell us with certitude at what stage of human development visual memories are sufficiently formed so as to perdure at least vaguely and effectively if sudden and total blindness should occur. Some psychiatrists believe that, in children blinded at the age of 2 or 3, there is already sufficient visual memory so that later concepts are influenced if not formed by it; others will put the age at 5 or later. At the moment, the fields of education and rehabilitation have very little substance upon which to work.

A further distinction is sometimes made between those whose personality was formed in the period of their blindness and those whose personality formation was completed before any loss of sight occurred. At the moment, of the rehabilitation centers for the blind in the United States, only three attempt to draw this distinction, and of these only two do so from a priori reasoning. The excellent rehabilitation center run by the Veterans' Administration at Hines, Ill., takes only those who lost their sight after the age of membership in the armed services, since its purpose is to rehabilitate only the veteran; although the distinction is made by chance rather than choice, some suspect that it is one of the factors responsible for the high success of the center.

OTHER IMPORTANT FACTORS

The person who would fully understand the variations within this field would have to consider the victim's age at the onset of cause as well as his age at the actual onset of blindness, present age, degree of vision, prognosis, cause of visual impairment (particularly hereditary factors which can cause resentment of parents or parental guilt, together with questions concerning one's own marriage; self-in-questions concerning one's own marriage; self-inducement; or inducement under guilt-laden circumstances, etc., as opposed, for example, to trauma in heroic circumstances), premorbid and postmorbid psychological states, and the presence or absence of other disabilities.

MULTIPLE DISABILITIES

The presence or absence of other disabilities is of particular importance to the total program of the NINDB since very often the additional impairments are neurological in nature. Recent studies indicate that whereas among retrolental fibroplasia (RLF) victims there are numerous children, now young people, who are normal in every way except for their

visual impairment, many others carry with them some congenital abnormality usually of a neurological kind. Apparently the incidence of these abnormalities in RLF children is approximately the same as in other infants born at the same stage of prematurity. Despite the fact that we still see an occasional child added to the rolls of the legally blind because of retrolental fibroplasia, most of us look back on the frightening days of the RLF "plague" as a bad dream of the past, while trying to do everything possible for the young persons blinded by it.

Our present major concern with regard to children has to do with the as yet unknown effects of the recent rubella (German measles) epidemic. Numbers are not yet clear to us, but we can be certain that there is an increase in the number of blind babies and that a number of these will be multiply handicapped. Only now are we managing to refine curricula and training programs for these multiply handicapped children, particularly for those with mental retardation and emotional disturbance. At the postschool rehabilitation level, the multiply handicapped blind are a currently serious source of worry and frustration.

THE GERIATRIC GROUP

Our discussion of age at onset of blindness concerned itself mostly with the very young, and "present age" was listed simply as a factor to be looked at. It is essential that new attention be given to that vast number of blind persons who are in the older age group—and also to those elderly persons who have serious visual impairments but who are not legally blind.

Although it has been known for two decades that the majority of blind persons are in the upper age brackets, and although it could readily be foreseen that the future was to bring a great increase both in the number of elderly blind persons and in the proportion of blind persons who would be elderly, the relatively new field of rehabilitation of the blind has been forced to concentrate its efforts on the rehabilitation of the young and middle-aged. It has had neither the time, the funds, nor the manpower to concentrate on this quantitatively most important area in rehabilitation—the geriatric group. Now various agencies are beginning to do studies in the area; there appears to be a trend toward closing homes for the custodial care of the aged blind and the blinded aging, so that they may be integrated into a sighted society; one of the remaining homes has put more emphasis on rehabilitation; and within the last 2 years, there has been established in the United States the first and as yet the only geriatric center for the blind, set up to give a period of evaluation to the total problems caused by combined aging and visual disability and then to proceed with a rehabilitation program designed to restore the elderly blind person to a fuller and more intensive life. What is at present needed is not only the increased funding of such centers, but some very thorough exploration and research so that, for such persons, blindness may not mean an end to living.

REHABILITATION IN THE WORKING YEARS

In the overview we have taken up to now, we have looked at various complicating aspects of blindness and called attention to little known complications in what appear to be simple definitions. Our limited look at rehabilitation has mentioned the multiply handicapped and briefly described the aging. Little has been said about that field normally encompassed by rehabilitation of the blind, the rehabilitation of blind persons between their late teen years and earlier or later middle age.

Although blindness does not kill, it often means an end of an active life—too often and unnecessarily. Unfortunately, too many persons who are blinded during active life do not know of the potential or even the existence of modern rehabilitation. Often, instead of finding the place where total rehabilitation is available to enable them to continue that active life, they are allowed to sit, dependent and deteriorating.

A working man, blinded in his prime, may have to fall back upon others to continue his very existence—an existence made far less attractive in terms of employment opportunities and his ability to enjoy innumerable activities. He often faces severe problems of emotional adjustment in accepting such restrictions. In our day, particularly in our poverty programs, we have discovered that the poor often do not know of medical and hospital resources available to them. In the field of blindness, we have known for some years that this lack of knowledge is not restricted to the poor. Society at all economic and educational levels has such deeply ingrained stereotypes about blindness and helplessness that too often even the most knowledgeable, including those in the medical professions, are not aware of the potential of blind persons who are given sufficient opportunity at the right time to receive full rehabilitation service.

It would be easy to blame rehabilitation programs for the blind for not letting this rehabilitation potential be better known, or to lash out at society for its stereotypes. Neither would help the situaion. Undoubtedly there is need for action on many levels to make the rehabilitation services which already

exist more widely known, and perhaps there is need of some study in depth to discover why those who should be knowledgeable have been kept from learning that blind persons properly rehabilitated can, to use President Johnson's words, have "the prime of life extended"—that these Americans can indeed in a great number of cases keep up useful, productive, and fruitful lives despite their major visual deficiency. As for international health and welfare, advanced rehabilitation centers in the United States receive a stream of visitors from the emerging countries; they stay for a brief period of observation or for a longer training period in order to bring back to their own countries what has been learned in rehabilitation centers for the blind in the United States in recent years.

EVALUATION OF FACILITIES FOR THE BLIND

At this stage, it is extremely difficult to list rehabilitation centers for the blind, although lists can be discovered. The present difficulty revolves around the different viewpoints, methods, and standards existing in different centers. Work for the blind has just reached a point where it is entering on accreditation. As with every approach to accreditation and the setting of standards, there is a certain degree of controversy, but for the most part professional workers in the field believe that we are at the beginning of a new and better day with the establishment of COMSTAC, an independent organization set up as a commission for standards and accreditation in the broad field of services to blind people. Within a few years, it should be possible for the ophthalmologist or other interested professional to learn through COMSTAC those agencies to which a blind person should be referred for the rehabilitation most suited to his needs.

Perhaps, at this stage, the one definite statement which can be made is that skill rehabilitation and psychological rehabilitation must go hand in hand. No attempt at solving external problems will be successful without an effort to solve internal problems, and conversely, it is fruitless to attempt to work merely with the internal problems without seeking to solve those which are external. Within the blindness rehabilitation field, there are varying degrees of emphasis, but probably all professionals in the field would agree that, whatever the emphasis, the two aspects must be treated. When this is done and properly done, with a total involvement of the blind trainee, we see one after another totally blind or severely visually handicapped person returning to take his role in the family and to secure a job and/or resume a professional role equivalent to that which he held before—in many cases, the same position.

DEVELOPMENT OF PROFESSIONALIZATION

This chapter could not possibly begin to outline the facets involved in the rehabilitation process which we have described elsewhere as one of pain and repeated crises, but one whose outcome can be worth every moment of pain and every crisis undergone.

World War II gave us the beginnings of our present rehabilitation outlook, together with the development of the Hoover cane and Hoover cane technique (the first systematic course in the use of a special cane for the blind). The Vocational Rehabilitation Administration furthered this technique by funding graduate education for trainers in the field, and brought the technique to untold numbers of blind persons by its selected demonstration grants in the area. More recently, it has begun to fund graduate training for "home teachers" of the blind. It has also given major assistance by funding training for rehabilitation counselors. Matching Federal funds to the States under the Social Security Act have helped to bring a new degree of professionalization to social workers in the field, and recent changes in Federal statutes have given new impetus to this professionalization. In consequence of this impetus at a training and what we might refer to as a "clinical" level, work with blind persons is reaching a level of competence hardly dreamed of two decades ago. There remains, however, the problem of research concerned with blindness—not the research in the prevention of blindness and its cure so well outlined in this report, but research concerned with assisting rehabilitation toward a fuller life for the person already blind or suffering from severe visual impairment.

INSUFFICIENCY OF RESEARCHERS

In the summary chapter at the beginning of this volume, the authors state: "yet, we discover that there are comparatively few research programs being conducted under NINDB auspices on rehabilitation and teaching methods for * * * the 400,000 legally blind or * * * the far larger group * * * who have experienced a significant visual loss. This is a consequence of the lack of trained research workers in this field, and the problems encountered in the definition of suitable research models."

True, there are trained research workers in this field, but the number is small indeed. In the Duane report [1] it was noted that "in 1963, throughout the

[1] T. Duane, *Ophthalmic Research: U.S.A.*, Report to the Trustees of Research to Prevent Blindness, 598 Madison Ave., New York, N.Y., 10022, 1965, p. 52.

entire nation, only 55 ophthalmologists and 82 basic scientists were devoting 70 percent or more of their time to vision research." In 1966, omitting the few researchers, including basic scientists, who more in and out of the field because of a specific grant, we would be hard pressed to discover a dozen trained researchers devoting 70 percent or more of their time to research in typhlology! [2] This brings us to a major field which is an interest of the NINDB and which the Institute and the NANDB Council are very much interested in assisting.

NEED FOR RESEARCH

These volumes have attempted to bring out the present status of research with regard to attacking the major causes of blindness and to give direction for the future day when these major causes will be overcome. Those working day and night with blind people are ready to back any massive attack to prevent blindness in the future.

We would hope for similar support from those seeking to prevent or cure blindness to assist in understanding and attacking the major causes of the disability which blindness brings. For the country has not yet committed its full resources to rehabilitation research for the blind we already have with us!

The purpose of this chapter is to seek the answer to the following questions: What are the major causes of the disability brought about by blindness and visual impairment? What are the best ways of attacking these problems? What should the NINDB be doing in order to assist (and stimulate) the scientific community in the attack on these problems?

Those who have written the previous chapters have behind them a mass of research material, most of it with the cold, clear facts of the hard sciences. This chapter must depend in a measure on the far less certain results of other types of research and the reports of human observers.

This is not to say that the field of typhlology has been devoid of research. See the chapter, "The Visually Handicapped," by Samuel C. Ashcroft and Randall K. Harley, for an excellent review of research and development contributions to the area of the visually handicapped. It is to say that altogether too much of our action for blind persons and for those with lesser visual impairments is based on hypotheses which, for the most part, have not been critically tested.

[2] Typhlology, from the Greek root *typhlos*, blind, is used to describe the science and art of work with the blind and the field which concerns itself with this science and art.

DESCRIPTIONS OF RESEARCH IN PROGRESS

One Government agency has been outstanding in its support of rehabilitation research, namely, the Vocational Rehabilitation Administration in the Department of Health, Education, and Welfare. While the NINDB has given support, its main thrust has been in the area of prevention and cure. The U.S. Office of Education and the NIMH have both made contributions, and the U.S. Veterans Administration has excelled in the area of prosthetics and sensory aids and supported valuable studies of the blinded veteran population.

An excellent study is to be found in *Blindness* 1964 (*1*), supplemented in the 1965 issue of the same annual (*2*). Particularly important is the 1964 study which, in its narrative, gives a background for the listings to follow and then breaks out research and demonstration projects on the subject supported by various government departments—"U.S. Government-Sponsored Research To Study Blindness," Switzer and Bledsoe. The article breaks into four major interests the work of the Vocational Rehabilitation Administration concerning blind persons. These interest categories are: (1) The work blind people do, (2) the readying of blind people to work (by whatever means, be it therapy, education, counseling, or any yet undreamed of process), (3) instruments of whatever sort which help to overcome or circumvent the handicap of blindness, and (4) training personnel.

WHAT REMAINS?

One reading the above list of interest categories encompassed by the Vocational Rehabilitation Administration might well wonder what areas remain as a responsibility of the NINDB. The answer lies in part in certain statutory limitations placed on the VRA because of its primary vocational interest. Admittedly, many of the things discovered by VRA-supported research intended to help those blind persons considered "feasible" for vocational rehabilitation have had a major spinoff for other blind persons who could never hope for rehabilitation in the vocational area. Yet there remain areas of research which the VRA cannot enter because of restrictions placed upon it.

The NINDB, with its broader charge, could readily move into these areas, and it is in a position to stimulate large numbers in the medical scientific community to make a major attack upon them.

TRAINING NEED

It is possible that the NINDB's greatest contribution to typhlology could be in the field of training

rather than in direct research. All workers for the blind accept it as a fact that, with few exceptions, both clinicians and researchers in the field of ophthalmology are so distant from the field of typhlology as not to be aware of current developments in that field, not to understand the life and the potential of the blind person, and too often not to be in any position even to refer him to the proper source for help. Some in the field of psychology have made the claim that this is almost necessary, that it is a personality defense essential to the ego protection of the ophthalmologist. To others, this is a completely unsupported statement, and one which they believe unfounded in fact. They would place the blame instead on a gap in the training of ophthalmologists. If this is so, then we can hope that the NINDB's training program support could give new training to a new generation of ophthalmologists, while at the same time training researchers whose interest would be in the study of blindness.

Leaving the "interest categories" of the VRA, we would place necessary research in blindness under six rubrics:

1. Definition of characteristics of the blind population;
2. Investigation of medical aspects of blindness (other than strictly ophthalmic);
3. Investigation of sensory processes in the blind;
4. Investigation of psychological aspects of blindness;
5. Investigation of adjustment to blindness; and
6. Instrumentation, particularly of the sophisticated variety.

DEFINITION OF CHARACTERISTICS OF THE BLIND POPULATION

In the first category, we find that the NINDB has already given some support to restudying the definition of blindness. The work done up to now has been helpful, but we are far from a solution of this problem. Involved in it is another problem scarcely touched: the evaluation of parameters of low vision. This need cries out for good research, and it is one where optic researchers could readily work in cooperation with trained clinical observers, both in ophthalmology and typhlology.

Within the intramural program of the NINDB, the Biometrics Branch has begun some extremely important epidemiological work under its model reporting area program. This has already been helpful to the typhlologists and, as it develops, will be of increasing help in giving us a better picture of demography as well as of morbidity and mortality statistics.

Examples of other studies which the NINDB could stimulate, fund by grant, or even contract for include: Unknown questions concerning the married life of blind persons (premorbidity and postmorbidity); the effects of blindness on siblings (bringing in both congenital blindness and early adventitious blindness); the effects of blindness and society's attitude toward blindness on the children of a blind parent; and the effects on marriage when a child is born blind or blinded at an early age. (Some might immediately equate some of the above studies with similar studies in the area of cerebral palsy, muscular dystrophy, etc., but in the opinion of at least some schools of psychiatry, blindness is a problem of a very specific sort, with its own special psychological concomitants.)

INVESTIGATION OF MEDICAL ASPECTS OF BLINDNESS

When we come to our second category, investigation of the medical aspects of blindness, one of our first concerns is diabetes. Earlier in this volume, in his chapter on "Diabetic Retinopathy," Dr. Leopold noted that diabetic retinopathy is an enigma, a frightening complication in the prolonged life of many individuals with diabetes mellitus. Blindness and disability from this cause in diabetic individuals who would otherwise be at the prime of life represents a major medical challenge. It is frightening to the typhlologist also, and a supreme challenge. In at least one rehabilitation center for blind persons in the United States, diabetes has over the last 2 years been the cause of approximately 50 percent of the blindness. Those reading this report are well aware of the numerous complications to be expected in this population. Yet the attempts at rehabilitation go on without major studies in depth psychology. There is little information on the effect of tactile sensory loss on braille learning. Preliminary work done at one center suggests the possible, though scarcely credible, hypothesis that in some advanced cases auditory acuity shows a relationship to blood-sugar levels, yet to our knowledge nothing has been done to substantiate or dispose of this hypothesis, despite its extreme importance for the safety of the blind diabetic. Some suspect that, in advanced stages of diabetes, the labyrinthine sense and kinesthesia suffer impairment to some degree; it would be important to know whether this assumption is true or false. The blind diabetic still does not have a ready solution to self-testing for glycosuria, although the importance of this need hardly be underlined. One well-known physician in the diabetes field has expressed his opinion that good rehabilitation of the diabetic blind person including both psychological and skill rehabilitation produces better control of

the diabetes and a longer life expectancy. Since in some ways this statement runs contrary to what some had predicted, it should be effectively researched. These are but a few of the possible areas of investigation which could be of great benefit to the blind diabetic.

There are limitless other possibilities for investigation under the same heading. Thus it would be extremely important to identify those retinitis pigmentosa strains which are connected with hearing loss and deafness, this both from a genetic and a rehabilitation standpoint. The field of geriatric rehabilitation of the blind is scarcely touched on in research literature. We know nothing, or next to nothing, about the rehabilitation of the blind aphasic and, to our knowledge, no one has investigated the visual rehabilitation of the hemiplegic with homonymous hemianopsia. Where is the investigation of the micturition problems of the blind male or the hygiene problems of the blind female?

INVESTIGATION OF SENSORY PROCESSES IN THE BLIND

As for the sensory processes in the blind, some work was done by earlier experimental psychologists, particularly in Europe, but our areas of ignorance remain great, for example: Sound localization, special hearing aids or even criteria for giving hearing aids to blind persons with hearing loss; the use of hearing to detect objects—some excellent preliminary work has been done here in the past, but now it seems more popular to attempt to get at the problem by studying "sonar" systems in bats, oil birds, and dolphins, rather than researching this matter with blind subjects; the olfactory sense in orientation; labyrinthine loss and restoration of balance confidence; the subconscious awareness of environmental cues; etc.

INVESTIGATION OF PSYCHOLOGICAL ASPECTS OF BLINDNESS

When we come to the fourth category, the investigation of the psychological aspects of blindness, we have a vast field which many have attempted to probe, but in which many believe that as yet we have scarcely begun to find the answers. Perhaps one of the most important contributions which the NINDB might make here would be to fund a major study or series of seminars simply to evaluate the "state of the art." Perhaps what we need most is the evaluation of the many psychometric studies and/or psychological tests which have been developed or partially developed, some of them in use and some of them simply lying on the shelf. Out of this could come validation studies and direction for further research. Perhaps this is the point at which to suggest that the NINDB might avail itself of the typhological strengths of the VRA in some sort of interdepartmental arrangement; interdigitation here and elsewhere in this whole field of typhology could strengthen the contribution of both agencies.

A few quick examples of other investigations under this rubric have to do with: Stress and the rehabilitation situation; investigation of means of overcoming the denial mechanism in blindness; numerous studies on the dreams of blind persons—congenital and adventitious—some from a depth psychology standpoint, others for better understanding of cortical function; a study of the effects of rehabilitation and/or of blindness itself on the personalities of those who have caused their own blindness in attempts at suicide; and so on.

INVESTIGATION OF ADJUSTMENT TO BLINDNESS

The fifth category, investigation of adjustment to blindness, is as vast a field as the investigation of adjustment to life. Despite the studies that have been made, we scarcely know the answers. One of the most widely circulated books on blindness at the moment attempts to analyze blindness, claiming to find some 20 losses (*3*). Although hopefully the book is of value in rehabilitation, anyone objective about it must note that it is filled with statements supported only by observation and even hunch. The day is not here, and we hope not near, when the importance of the trained human observer no longer exists—but we have advanced too far in the field of scientific discovery to allow the adjustment of 500,000 legally blind persons or a million visually handicapped persons to depend on the observation of one individual or any group of individuals.

Without bothering to give even a few of the multiple questions concerning the adjustment of blind persons, we simply state our opinion that this is a major responsibility of a government interested in its citizens.

INSTRUMENTATION, PARTICULARLY OF THE SOPHISTICATED VARIETY

We entitled this final category as "instrumentation, particularly of the sophisticated variety," avoiding a temptation to refer to the "glamor projects." At the moment, there are three important instruments which have proved their value in helping the blind individual achieve mobility, viz, the human guide, the dog guide, and the cane. While we look for new means of achieving independent mobility,

it is extremely important that we not neglect the study of these existing devices. Workers for the blind are extremely interested in the devices of a future day and hope that their development may be speeded, but in the meantime, one simple bit of instrumentation only now being studied is a rather ancient one, the blind person's cane. Thanks to some studies already done, we know some of the characteristics which a cane must have and some of the compromises which may have to be made in finding the optimum cane. But in our sophisticated day we have still not developed that simple instrument.

The worker in the field of blindness is torn. He knows that the day of electronic reading devices, which in one form or another will "translate" the printed and even the handwritten word into something intelligible to the blind, is not far off. He wants promising studies in this field to be funded well and to be undertaken by the best centers and the best researchers. Yet he sees the field of academic research leaving behind the immediate and imperative problems of the day to work on those areas which are "way out." Sophisticated instrumentation is important and must be given its proper high priority in any research in typhlology, but a similar if not equal priority must be given to learning about blind people and to helping them to live today and tomorrow while preparing for the world of the day after.

RESEARCH DIFFICULTIES

Unfortunately, in many of the matters we have touched upon in this chapter, there are almost as many variables as there are cases. Where this is true, even the layman in the field of research knows that the possibilities are only two. One is to give up the attempt to research and to rely wholly on clinical observation. The other is to research what are believed to be the most important variables. The very words "believed to be" take us away from the hard facts of research. Here it seems that the answer must depend on two groups: The necessarily subjective, but hopefully knowledgeable group, consisting of those long in proximity with blindness, and a relatively objective group of researchers in both the hard and the soft sciences, who will look to see what truly are the important variables, or those most likely to prove so.

RECOMMENDATIONS

My recommendations for future efforts by the NINDB in the field of typhlology are:

1. An interdepartmental planning group which would include at least the VRA representatives, and perhaps persons from other areas within the government;
2. An ad hoc advisory committee to take an overall look at this phase of the Institute's responsibility;
3. Consideration by NIH of a special study section concerned with this field (and perhaps other fields of rehabilitation);
4. If it should be recommended by the ad hoc committee, a major program of contracted services in different aspects indicated in this chapter;
5. Introduction of training in typhlology into the ophthalmological training programs sponsored by the Institute;
6. Similar training given to researchers in optics;
7. The establishment and publicizing of postdoctoral fellowships and new career development awards in the field of research concerning the subject; and
8. The establishment of one (or more) national rehabilitation center(s) for the blind and partially sighted.

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Chapter 21—THE VISUALLY HANDICAPPED

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INTRODUCTION

The space age and related technological advances were reflected in research and development contributions to the area of the visually handicapped during this review period. Especially pertinent contributions were related to mobility and communication. Technological research exceeded behavioral research by virtue of the sophisticated talent recruited and the financial support provided by government, industry, and business; however, there were encouraging signs of improvement in the amount and quality of research in education and psychology. Increased financial support for behavioral research has ameliorated one serious problem, but the scarcity of interested and competent research personnel remains critical. This review reflects the continuing need for more integrated and programmatic research designed to answer questions significant for education.

This chapter reviews the period since the review by Lowenfeld (1963b), a shorter time interval than that covered by the reviews in 1941, 1953, and 1959. Comparisons of the work discussed in these reviews show growth of interest and acceleration of activity in the field and in related technological research. The present review is not exhaustive but rather includes selected work illustrative of the type and quality of activity during the review period.

GENERAL ASPECTS OF THE VISUALLY HANDICAPPED

Two recent general works merit special attention since they reveal the emphasis on technology. "The Proceedings of the International Congress on Technology and Blindness" (American Foundation for the Blind, 1963) presented the proceedings of the International Congress on the topic in four volumes: "Man-Machine Systems," "Living Systems," "Sound Recording and Reproduction and Adapted and Special Purpose Devices," and "Catalog-Appendix." The proceedings represents an important landmark and sourcebook in the field, but the work suffers from the necessary brevity of the widely diverse presentations and the lack of integrative and summary material. "Human Factors in Technology" (Bennett, Degan, and Spiegel, 1963) includes a section on Human Factors in Sensory Supplementation composed of eight brief chapters on tactile and aural communication and mobility. The theme of this book—the congruity or compatibility between man and technological society—provides a significant model for conceptualizing and researching the problems of matching human factors in visually handicapped individuals with cultural artifact and custom.

Several useful general works have appeared or have been reprinted. Ashcroft (1963a) contributed a research-oriented chapter on the education of visually handicapped children. Lowenfeld's (1963a) chapter on psychological aspects was revised and his book "Our Blind Children" (Lowenfeld, 1964) was reprinted with an additional chapter on adolescence. "Blindness" by Zahl (1962) was reprinted after having been unavailable for many years.

"Blindness" (American Association of Workers for the Blind, 1964, 1965), a new annual, was another important general contribution. These annuals classified and gave the purpose of research supported by the following governmental agencies: (*a*) National Institute of Neurological Diseases and Blindness, (*b*) National Institute of Mental Health, (*c*)

U.S. Veterans Administration, (*d*) U.S. Office of Education (Cooperative Research Branch, Research and Demonstration Projects Concerning Blindness), and (*e*) Vocational Rehabilitation Agency.

Data on research grant funds by fiscal year for the Vocational Rehabilitation Administration (VRA) (American Association of Workers for the Blind, 1964) illustrated growth from $32,294 in 1955 to $735,200 for 1964, with a total for the 10-year period of more than $4 million. VRA research was categorized in four major areas: The work blind people do, the readying of blind people to work, instrumentation to overcome or circumvent the visual handicap, and people who work for the blind. The second area is particularly germane to education since it includes the 23 optical aids demonstration projects.

Graham and Clark (1964) indicated that wide socio-politico-economic implications have been reflected in the research and development interests of European countries. Brief observations were reported on work in mobility, reading machines, braille production, sensory processes, and vocational aspects.

A monograph by Jones (1963) summarized recent developments in the field of educating visually handicapped children. Data were presented on the number of school systems reporting programs and the number of children registered to participate in the Act to Promote the Education of the Blind. Incidence figures were reported as "one visually handicapped child for every 1,000 to 1,500 * * * and one blind child for every 3,000 to 4,000" school age children. Projected estimates beyond 1970 indicated higher total numbers of visually handicapped children but a decrease to 1 in every 7,000 to 8,000 in "the prevalence of those considered by the schools as blind * * * "

An important new publication, the "Research Bulletin" (American Foundation for the Blind, 1962), inaugurated in 1962, emanated from the International Research Information Service (IRIS). The Bulletin is compiled by the Division of Research and Statistics of the American Foundation for the Blind. Among valuable recent editions was the "Bibliography of Mobility Research and Mobility Instrumentation Research" ("A Provisional Bibliography") (American Foundation for the Blind, 1964), which included 355 items.

Nolan's (1963b) review of behavioral research on visually impaired persons was a valuable contribution. Reviewed were illustrative studies in such areas as education, measurement, personal-social development, and physical performance. The review stressed lack of integration of research; the normative and comparative nature of previous work; disappointing quality of design, analysis, and reporting; and the paucity of research on partially seeing children. The most productive integrated educational research effort during the period continued to be that of the Department of Educational Research of the American Printing House for the Blind. Annual reports (Nolan, Morris, and Kederis, 1964; Nolan and others, 1965) provided an excellent source of information on this continuing program. The report for 1964 indicated that the same general emphases pursued previously were being continued; these were research on tactual and auditory communication, mathematics instruction, and educational measurement. The Department provides an important service through its "Bibliography of Research on the Blind" (Nolan and Morris, 1964a). This supplements Lende's (1953) bibliography but differs in that it lists only research in which data were collected and reported.

Identification and Definition

A significant development for research was the Model Reporting Area for Blindness Statistics (MRA) (Goldstein and Goldberg, 1962). The MRA was developed by the Biometrics Branch of the National Institute of Neurological Diseases and Blindness with the cooperation of a number of agencies concerned with visually handicapped persons. At least 10 States were voluntarily included in aspects of the MRA project since they had registers of blindness and had adopted standards for obtaining uniform data to facilitate cross-State comparisons of causes, incidence, and prevalence. A standard classification system and a new uniform eye report form were developed by the National Society for the Prevention of Blindness (Gibbons and Hatfield, 1964) as part of this study. Although the first data (Goldstein and others, 1964) from the MRA on incidence by cause of blindness for 1963 were disappointing, the major problems (such as uniform reporting) have been identified and solutions can be sought.

Jones (1963), reflecting the trend toward educational rather than medical or legal definition, defined visually handicapped children as those "who either have no vision or whose visual limitations after correction result in educational handicaps unless special provisions are made." He indicated that "sight utilization rather than conservation * * * has come to be stressed." Decisions regarding the placement of a child in terms of special programs are now being based on the "extent to which the child's visual impairment *handicaps him in school* rather than on the extent of visual loss."

Medical Aspects

Hatfield (1963) continued the useful series of studies by the National Society for the Prevention of Blindness on causes of blindness in schoolchildren.

Unfortunately, the data continued to be seriously out-of-date before publication. The 1963 analysis of the data for 1958–59 suggested that the rate of occurrence is expected to decline but that the prevalence would increase due to population growth. Infectious diseases and injuries as causes dropped 79 and 58 percent, respectively, during the last 25 years; prenatal factors and unknown causes continued at high levels. It can be hoped that the MRA will significantly improve the accuracy and promptness of data on the incidence and causes of visual handicaps.

The rubella "wave" (Waterhouse, 1965) threatens to follow the retrolental fibroplasia wave as a cause of blindness in preschool children. Educators are already aware of the changing nature of the population of visually handicapped toward an increase in multiple handicaps. The rubella wave will undoubtedly increase the number of severely multihandicapped children with serious eye disorders. Proposed preventive measures, such as exposure of young females to measles and the use of vaccines, require further research.

The collaborative Perinatal Research Project (U.S. Department of Health, Education, and Welfare, 1963) being carried out at the National Institute of Neurological Diseases and Blindness (NINDB) and 15 medical centers was reported to be successfully isolating and cultivating the virus causing rubella. Experimental vaccine has become available. The NINDB found that some drugs such as cortisone and corticosteroids were causing eye disorders (cataracts and glaucoma), but in spite of these problems advances have been made in drug and chemotherapy. As another example of progress in medical research, pleoptics—a type of light therapy—has shown promise in treating amblyopia. Masland (1964) indicated that the NINDB was spending $13 million a year for blindness research. From 1952 to 1964 the number of full-time practicing ophthalmologists increased 50 percent, from 2.2 per 100,000 to 3.3. Kane (1963) described electronic computer applications for classifying and diagnosing eye problems. Topographic and etiologic classifications of eye problems are included with "some 90 fields of information about each case," in the perinatal study.

From a study of visual perception in strabismus and amblyopia, McLaughlin (1964) presented evidence "that the underlying disorder in the strabismus-amblyopia syndrome is a previously unrecognized anomaly of visual perception * * * ." The study, which took a psychological view of a problem usually considered exclusively from a medical standpoint, indicated that "objects as seen from one eye are perceived as being unreal" and are eventually suppressed. A psychological approach to remediation was suggested as fruitful for selected cases.

Technological Research

Mann (1964) reported on the establishment of a Center for Sensory Aids Evaluation and Development which is engaged in evaluating and redesigning a high-speed electric braillewriter, utilizing teletype and monotype tape for typesetting as inputs for braille transcription or mechanical readers, converting typesetting tapes to spoken words, developing collapsible canes and guidance devices for mobility, and in completing other projects.

The development of a Tactile Research Center was reported by Bliss and Crane (1965). Practical applications of research findings are being sought to provide blind or deaf-blind individuals with a substitute for sensory loss. An example of such application is the transmitting of alpha-numerical navigation information to astronauts without the use of visual or auditory channels. Studies have also involved the development of tactual displays activated by photocell scanners. Vibrating pins and air jets have been used to produce small arrays of as many as 100 tactual stimuli. These "sensory translation" devices have been used to generate English texts in various alphabet forms. Visually handicapped subjects have reached reading rates of about 30 words per minute in relatively short training periods. Among interesting results was the finding that by reducing the structure of the letters, in terms of the number of stimulator points, "subjects could learn to recognize these 'abstracted' letters with great accuracy and also with considerable speed." The research includes extremely limited numbers of subjects and is of a pilot study nature.

The Russian reading machine (Graham and Clark, 1964) is a refinement of the optophone principle. It uses an eight-channel scanning system to read inkprint characters. The instrument emits an auditory display that produces a musical chord. The Russian research, which is based on 12 students in a school for the blind, produced the surprising result of 300 to 400 characters per minute, the apparent equivalent of 30 to 40 words per minute, assuming the Russian language would average 10 characters per word. (The present writers sampled 275 words of running Russian text and found the words to average more nearly six characters.)

Such burgeoning technological developments have exciting potential for solving some of the problems of visually handicapped individuals. However, no significant practical applications are yet available and more applied research is urgently needed.

PSYCHOLOGICAL ASPECTS

Attitudes

Recent research regarding attitudes toward visual handicaps deals with the nature and measurement

of attitudes of the sighted population. Bateman (1962) found that sighted children who had previous experience with blind children were more positive in their appraisal of abilities of blind children than were those without such previous contact. Bateman (1964) also noted that the attitudes of adults were not affected by personal contact with blind persons but that they were improved by information giving techniques.

Whiteman and Lukoff (1964) administered a questionnaire to 85 evening college students and an abridged vesion of the same instrument to 65 social work students. Five attitudinal factors were identified: (*a*) The degree to which the respondents have negative attitudes toward blind people, (*b*) the degree to which the respondents see blind people as socially competent, (*c*) the degree to which blindness is perceived as threatening or frustrating, (*d*) tendencies to be protective toward blind people, and (*e*) readiness for personal interaction with blind people. Jones and Gottfried (1962) confirmed results of previous studies revealing that teachers rank preference for teaching visually handicapped children near the bottom when ranking the desirabilities of teaching in the areas of exceptionality. Rusalem and Rusalem (1964) indicated that a group of college students had tendencies toward stereotyped attitudes characterizing deaf-blind persons as unhappy, envious, and devoted to religion.

Such recent studies have tended to confirm earlier beliefs concerning stereotypes and attitudes of the sighted toward blindness. Few studies have been reported, however, in which attempts were made to change attitudes. More research is needed to validate scales and to determine the extent to which visually handicapped individuals are accepted or rejected in school, at work, and in various types of social activities and organizations.

Tests and Appraisal

Lowenfeld (1963b) cited the urgent continuing need for supplementing tests of verbal intelligence with performance tests. Some evidence suggests that progress is being made in this regard for adults, but relatively little similar work for children has been reported.

Davis (1962) reviewed the assessment of intelligence of visually handicapped children. He described plans for the long-awaited adaptation and standardization of the 1960 "Stanford-Binet" on 2,500 blind children and young adults, ages 3 to 21. The delay is critical in availability of this instrument to replace the long-outdated "Interim Hayes-Binet Test of Intelligence for the Blind." Newland (1964) pointed out the need for more research on the prediction and evaluation of academic learning. The blind learning aptitude test, which Newland has been developing, has the virtue of being empirically developed in contrast to the usual practice of adapting tests for the sighted for use with visually handicapped individuals. There has been extreme delay in development and publication.

The "Haptic Intelligence Scale for the Adult Blind (HIS)" (Shurrager, 1961) was adapted partially from the performance scale of the "Wechsler Adult Intelligence Scale" with special supplements. IQ's for visually handicapped individuals must be used with caution and cannot be assumed to have the same meaning as do those for seeing individuals because of great variability in subtest scores. A tactual form of the "Raven's Progressive Matrices" has been developed by Rich (1963), who studied the validity of modified designs for tactual perception by blind children ages 6 to 15. Low but significant correlations were found with "Wechsler Intelligence Scale for Children" verbal scores, and a high correlation was obtained with academic achievement for children above age 11.

Several tests related to braille reading have been developed. Nolan, Morris, and Kederis (1964) described a roughness discrimination test and its usefulness in predicting success in learning to read in braille in the first grade. Woodcock and Bourgeault (1964) developed a series of diagnostic tests for readers of braille. These tests, standardized on 1,500 subjects, were designed to measure mastery of the elements of grade 2 literary braille and the Nemeth code of mathematical notation.

A number of intelligence and achievement tests were reported to have been adapted to braille and large type. Examples (Nolan, Morris, and Kederis, 1964) were new forms of the 'Stanford Achievement Tests," the 'School and College Abilities Test (SCAT)," and the "Sequential Tests of Educational Progress (STEP)." Pearson (1963) modified the SCAT in large print and braille for a study with blind and partially seeing children in seven residential schools. The "Scholastic Aptitude Test (SAT)" standardization for visually handicapped high school students was improved with norms based on scores from larger numbers (College Entrance Examination Board, 1965) than heretofore available.

Mueller (1962) found that the "Peabody Picture Vocabulary Test (PPVT)" could be used without adaptation for partially seeing children having visual acuities from 20/70 to 20/200 but that the larger preliminary version was better for children with less vision. Bateman (1965) concluded that the "Illinois Test of Psycholinguistic Abilities (ITPA)" could be used for children with visual acuities from 20/20 to 20/200. However, significant differences were found between visually handicapped and normally sighted children on five factors: Visual decoding, motor encoding, visual-motor sequencing,

visual-motor association, and total language age. Land and Vineberg (1965) used the "Bialer-Cromwell Children's Locus of Control Scale" and found significant differences between blind and sighted children on only two items of the scale and no differences between blind children from day and residential schools. It had been hypothesized that sighted and local day school blind children would show more internal control than blind children from a residential school.

Bauman, Platt, and Strausse (1963) reported the development of an adolescent "Emotional Factors Inventory (EFI)" which was standardized on a relatively small sample of residential and day schoolchildren ages 13 to 18. This instrument was similar to the EFI developed earlier for adults. Differences found between residential and day schoolchildren might be attributed to selection factors or socioeconomic status rather than to school placement (Bauman, 1964).

The use of projective tests with visually handicapped individuals increased in recent years to the extent that Lebo and Bruce (1960) reported 20 such tests having been discussed in the literature.

Abstract Functioning and Concept Development

Rubin (1964) compared abstract functioning by testing the hypothesis that congenitally blind adults would be significantly inferior to adventitiously blinded persons or to sighted volunteers. Significant differences were found on one of four tests of abstraction. Harley (1963) obtained significant relationships in a study of verbalism and age, intelligence, and experience among residential school blind children. No significant correlation was found between personal adjustment and verbalism. The study indicated that visually oriented verbalism was no longer the problem described by Cutsforth (1951) but that verbalism caused by lack of concreteness and firsthand experience continued to be an important problem in the education of blind children.

Foulke (1964a) reported on a multisensory test of conceptual ability developed to provide an indication of the kinds of sensory stimulation to which the blind child responds and the extent to which such stimulation provides information leading to concepts. The test consisted of 14 blocks to be sorted according to such common characteristics as texture and shape. Imamura (1965) compared the behavior of preschool seeing and blind children and concluded that the latter were more demanding of care and attention. Differences were discovered between reactions of blind and sighted children to similar types of parental behavior. It was concluded that self-reliant children from both groups had mothers who gave the attention sought.

EDUCATION

Two significant surveys were reported concerning educational programs for visually handicapped children. Jones and Collins (1965) disclosed the results of a survey conducted by the Division for Handicapped Children and Youth of the U.S. Office of Education on 353 local day school programs and 54 residential schools. Trends in placement practices were noted toward: (*a*) More complete integration in regular public school classes, (*b*) more combination units of local day and residential schools for blind children, (*c*) more functional and flexible pupil placement, (*d*) increased provision for multiply handicapped children, and (*e*) provision for print reading experience for children with low vision before determining the medium of instruction.

Danwalder (1964) conducted an extensive national survey of existing industrial arts and vocational education training programs in residential and day schools and of employment practices. Among the findings was the report that 96 percent of the alumni of one residential school believed offerings in vocational training should be increased. A tendency was noted for some schools to reduce emphasis on chair caning, weaving, and mattress making and to place more emphasis on such subjects as sheet metal working, automabile mechanics, and electrical shop. An earlier study by Bauman (1963) provided a detailed analysis of recorded personal interview data on 434 professional and business persons. Pertinent findings were presented under the following headings: basic life characteristics, visual characteristics, school history, professional choice and experience, and related characteristics.

Results of a survey (Jones, 1965) of library services in residential schools in the United States and Canada were interpreted to indicate general inadequacy of facilities, books, services, finances, and trained librarians.

Recent research in education has been concentrated in the areas of listening, braille reading and writing, and sight utilization. Limited research in mathematics and mobility has been reported.

Listening

Nolan (1963a) compared learning achieved through listening with that achieved through braille reading. In a study using braille-reading subjects from grades 6 to 10, he found that information could be obtained through listening in one-third of the braille-reading time without loss in comprehension. The need for more research on this topic was stressed.

Coffey (1963) attempted to determine the value of programmed instruction for blind junior and senior high subjects. No difference was found when aural

and braille modes of presentation were compared; however, the junior high group profited most from opportunities to make oral rather than braille responses. Samways, Andres, and Klaus (1964) compared braille and tape-recorded presentations of a programmed instruction unit with adults and children. The auditory mode proved to be better, but it emphasized that the tape had been specially adapted for use by blind persons. Hartlage (1963) found no difference in listening comprehension between matched pairs of blind and sighted high school students.

McLain (1962) studied two methods of producing rapid speech or speech "compression," in which the playback time is shorter than the recording time. Using 46 percent compression (325 w.p.m.) with children from grades 2 to 7, the pitch-altering method was found inferior to the speech-sampling method which maintained the pitch of the original recording. Foulke and others (1962) compared reading in braille with listening to rapid or compressed speech among 291 braille readers from 11 residential schools and found no significant loss in comprehension of literary material at speeds up to and including 225 w.p.m. No significant loss in comprehension resulted when scientific material was presented at rates as high as 275 w.p.m. Bixler and Foulke (1963) concluded that research in speech compression was limited by the nature of the equipment and methods used to record materials. Foulke (1964b) reported that comprehension fell off rapidly beyond 275 w.p.m. and that there was no proof that comprehension improved with training.

Braille Reading and Writing

Ashcroft (1962) reported the development of "Programmed Instruction in Braille" (Ashcroft and Henderson, 1963), a book of planned lessons for adults or children who have previously read print. This book presents braille "contracts" in small, sequential steps and keys for immediate reinforcement of the student's correct responses. A programmed manual for instructing volunteers in the use of an electromechanical system for braille transcription and reproduction (Woodcock, 1963) is being compared with two other approaches to transcriber training. Development of an electric version of the Perkins braillewriter was also included in this study.

The effects of familiarity, wordlength, and orthography as related to perception in braille reading were studied by Nolan and others (1965). The number and position of dots in braille words were found to have significant effects upon recognition time. Word familiarity and number, position, and type of contractions combined in complex ways to affect recognition time. The study raised serious questions regarding the whole-word approach to teaching reading to blind children. Further work is needed on the same factors when the stimulus materials are presented in context.

Morris and Nolan (1963) studied the discriminability of tactual symbols. Results on braille readers in grades 4 to 12 indicated that grade-level differences exist in ability to identify symbols. Mechanics of reading in braille were examined by Foulke (1964c). It was found that the forefinger reads best and that the effectiveness of each finger falls off rapidly as the little fingers are approached.

Weiner (1963) investigated the tactual perception skills involved in reading braille and found that good braille readers possessed superior tactual perception. The study produced no significant correlations between MA, CA, IQ, or reading achievement and tests involving tactual perception.

Nolan and others (1965) reported no significant increase in braille-reading rates using controlled exposure devices with subjects representing various levels of reading speed. Practice encouraged by monetary reward was continued for 20 days at 1½ hours per day. Flanigan (1964) evaluated the efficiency of using a machine-paced teaching device in accelerating the speed of reading braille. No significant increase in reading speed was found. Differences were found in the number of retracings in the reading process and the number of words read weekly on the machine.

Sight Utilization

Massie (1965) analyzed recent research concerning the education of partially seeing children and noted a need for more research in such neglected areas as low-vision aids and communication media. One of the most exciting developments in the area was research concerning more effective use of small degrees of remaining vision. The Jones (1961) study documented the fact that large numbers of children with 20/200 vision or less were reading print and that a different emphasis was placed on this medium in day as compared to residential school programs. Nolan (1964a) replicated the Jones study and noted that the number of legally blind print readers increased by 2,536 or 5 percent between 1960 and 1963. He also noted an increase of 12 percent among residential school students who had vision described as "object perception," or better, who were registered as print readers.

Barraga (1963, 1964 a, b) studied the effects of specialized instruction on the visual behavior of children being education as braille readers. Substantial gains were found in the ability to use remaining vision among children in the experimental group. It was concluded that visual stimulation programs could be valuable in teaching low-vision children to use their remaining vision more effectively. Ashcroft,

Halliday, and Barraga (1965) replicated the study, confirmed the previous results, and recommended extending the treatment further to general practice with low-vision children.

Gibbons (1963) reported on the use of low-vision aids among 500 low-vision patients in 40 clinics. Thirty-five percent of the patients showed significant improvement in vision and continued to use their special lenses. Research is needed to determine how a greater proportion of such patients can be properly fitted and assisted to learn to use these aids effectively. Robertson (1963) described a survey of 42 clinics and indicated that more than half of the children examined in these clinics received optical aids and that preschool children were seen in a majority of the clinics. Followup studies on such children are needed.

Karnes and Wollersheim (1963) found the psycholinguistic processes involving visual and motor abilities to be inferior to the auditory and vocal abilities of partially seeing children. Bateman's (1963) work indicated that children with mild visual defects tended to read less well and to make more types of errors in relation to grade placement than did children with more pronounced defects. Many children appear to have entered the special program for the partially seeing because of undiagnosed reading or learning problems rather than because of vision problems.

Mathematics

Nolan, Morris, and Kederis (1964) reported the results of an experimental program in modern mathematics adapted for visually handicapped children. Achievement of students in five residential schools exceeded that of children in control programs by 3 to 6 months when grade averages were compared. A replication of the previous study (Nolan, 1964b) showed that the majority of braille students in experimental programs scored at or above their placements in grades 1 to 4. In associated research (Nolan and Morris, 1964b) the use of the Japanese abacus as a computational aid was explored; average skill improved as much as 66 percent over an 8-month period with a group of residential junior high school pupils.

Mobility

Rehabilitation of the war blind stimulated interest in mobility training for adults and later for children. Many articles have been written stressing the importance of mobility, but paradoxically there is a dearth of research in this area. Several extensive studies are now in progress, as reported in *Blindness,* 1964 (American Association of Workers for the Blind, 1964). Much activity in this area has been concerned with technological development of specialized detection devices; several studies can be cited that illustrate various kinds of research activity. Winer (1962) found positive correlations between intelligence and personal adjustment with the use of auditory cues among 22 blind adults. Hunter (1964) noted that blind persons were poorer than normally sighted persons in ability to manipulate themselves and obstacles in space. Riley, Luterman, and Cohen (1964) discovered a significant correlation between hearing ability and mobility performance in blind persons. Mickunas and Sheridan (1963) reported on the development of an obstacle course that was successfully used in evaluating mobility behavior of blind subjects.

THE MULTIPLY HANDICAPPED

Many articles have appeared concerning the development of programs for multiply handicapped blind children, but there is very little research on this group. The research available is largely limited to surveys. Several studies supported by the Division on Handicapped Children and Youth of the U.S. Office of Education are under way that should contribute important knowledge.

Dauwalder (1964), in a survey of ophthalmologists, reported an incidence of 24.52 percent for the multiply handicapped among the totally blind, and increased numbers were forecast for the next 5-year period. The Jones and Collins (1965) survey found a trend toward more provisions and school programs for multiply handicapped children.

Root (1963), and Cruickshank (1964) discussed problems of finding adequate services for multiply handicapped children and raised questions to be considered by educators who wish to evaluate the effectiveness of services. Cruickshank emphasized the importance of the residential center and defined roles that must be assumed.

Elonen and Zwarensteyn (1963) described a summer program for multiply handicapped children at a residential school for the blind, and Elonen and Polzien (1965) reported successful results from the program after four summer sessions. Cicenia and others (1965) described the program conducted in the unit for the blind at the Johnstone Training and Research Center. Donlon (1964) outlined the roles of various disciplines as they combined efforts to evaluate the multiply handicapped group at the Syracuse Center for the Development of Blind Children. Davidow (1962) reported subjectively determined gains in four areas of social behavior in a study of 15 mentally retarded blind children. Miner (1963) found speech defects among 33.8 percent of 293 visually handicapped children in two residential

schools but discovered no differences between boys and girls or between braille readers and print readers. Selection factors and institutionalization were not controlled. Haspiel (1965) studied early developmental data on 60 disturbed visually handicapped children. Similarities between this population and sighted schizophrenic and/or autistic children were noted. Deficient language, speech, and auditory functioning appeared to be used as a defense mechanism against an unacceptable environment. There appeared to have been a marked absence of babbling among the children at the preverbal state, and it was concluded that verbal interaction between parent and child was lacking for the emotionally disturbed blind child. Weinberg (1964) investigated the incidence of stuttering among blind children in residential schools and found it to be within the range of the normal population.

Stone (1964) noted two types of mannerisms ("blindisms") among mentally retarded blind children. Vigorous rocking was characterized as a withdrawal type of mannerism that served to block out environmental stimuli. Handclapping, which occurred on heightened contact with and pleasure in the environment, was considered an alerting type of mannerism. Differences in the two types were recorded in EEG patterns, with more rapid movements during alerting types and slower tracings during withdrawal types. Cohen (1963), in a study of 43 retrolental fibroplasia children from Chicago, noted that 36 or 37 EEG's showed abnormalities. Lairy and Netchine (1963) studied EEG patterns of partially seeing, blind, and seeing children and concluded that differences found in patterns might be "a functional expression of the oversolicitation of a cortical area," and that these differences might "play an indirect part in increasing the difficulties in achieving perceptual-motor efficiency * * * ." It would seem that other investigations of these possibilities should be pursued.

The number of general articles and surveys indicated greater awareness of the problems of multiply handicapped children and may stimulate more methodologically adequate research. As Cruickshank (1964) observed, it is important to stress the individual needs of each child rather than the categories of handicapping conditions. The low incidence of children who are blind and mentally retarded, blind and emotionally disturbed, or blind and orthopedically handicapped presents problems to the educator and researcher that may require an individual approach to each child.

SUMMARY AND CONCLUSIONS

As indicated in a recent article (Ashcroft, 1963b) there seems to be "a new era in education" but "a paradox in research." There is evidence of some preoccupation with status studies and test development, though there are unconscionable delays in completion and publication of the latter.

Urgently needed are: (*a*) Studies that examine assumptions apparently underlying traditional approaches (e.g., approaches to reading); (*b*) intervention studies to bring about behavioral change and to evaluate the efficacy of different educational procedures (activity as opposed to didactic or preceptive methods); (*c*) process studies (e.g., concept development and learning to utilize residual vision and optical aids) rather than characteristics studies (comparing visually handicapped and seeing children); (*d*) studies of evaluative devices or methods (different from adapted conventional tests); (*e*) human engineering approaches to the development of aids and teaching materials (matching tangible apparatus to human factors rather than adapting persons to machines); (*f*) applications of technological developments (reading machines and guidance devices); and (*g*) evaluations of teachers and program effectiveness and teacher preparation. A new era in research is needed to match the new era in education.

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glossary
part IV

GLOSSARY

Vision and Its Disorders

[This glossary is reproduced with the kind permission of Research to Prevent Blindness, Inc. It was presented as part of a Science Writers Seminar held November 6–9, 1965.]

A

Accommodation — The ability of the eye to adjust for various distances.

Acetylcholine — A chemical compound which is essential for the transmission of nerve impulses.

Acrylic — Plastic.

Acuity, visual — Expression of acuteness of vision.

Albinism, ocular — A deficiency of pigment in the eyes.

Amaurosis — Blindness occurring without apparent lesion of the eye.

Amblyopia — Impairment of vision with no detectable organic lesion.

Ametrope — Imperfection in vision.
Imperfection in the refractive powers of the eye.

Anabolic — Constructive as opposed to destructive metabolism.

Aneurysm — A sac formed by the dilatation of the walls of an artery or vein and filled with blood.

Angiitis — Inflammation of a vessel.

Angioma — A tumor whose cells tend to form from blood or lymph vessels.

Angle of anterior chamber — Junction between iris and cornea through which the aqueous flows.

Angioid streaks — Bands appearing in the retina often associated with systemic disease.

Aniridia — Absence of the iris.

Aniseikonia — A condition in which the image of an object as seen by one eye differs in size and shape from that seen by the other eye.

Anophthalmic — Absence of the eye.

Antibody — Part of defense mechanism.

Antigen — Substance which induces formation of antibodies.

Aphakia — Having no lens in the eye; e.g. after cataract removal.

Applanation tonometer — A device for measuring intraocular pressure. The estimate is obtained by measuring the area of the cornea flattened by a known weight, or by determining the weight necessary to flatten a known corneal area.

Aqueous humor — Fluid in the anterior chamber of the eye.

Arcus senilis — A white ring around the margin of the cornea especially in the aged.

Asthenopia — Weakness or tiring of the eyes, dimness of vision.

Astigmatism — Variation in lens power in different meridians resulting in a defective optical image.

Atropine — Paralyzes parasympathetic nerve action; applied locally to the eye to dilate the pupil and paralyze ciliary muscle for accommodation.

Autograft — Transplant one tissue of an individual back to the same individual.

Autoimmune — Allergy to one's own tissue.

Axon — Nerve fiber.

B

Bacteriophage — A bacterial virus.

Biomicroscopy — Microscopic examination of the cornea or lens with a slit lamp and corneal microscope.

Blepharitis — Inflammation of the eyelids.

Blepharospasm — Spasm of eyelid muscles.

Blindspot — Normal defect in visual field due to position at which optic nerve enters the eye.

Bulbar — Referring to the eyeball.

Buphthalmos — Enlargement of the eye.

C

Canaliculus (lacrimal) — Narrow tubular passage—tear duct.

Canthus — The angle at either end of the slit between the eyelids.

Carbonic anhydrase inhibitor — A chemical compound; e.g., Diamox, which suppresses the formation of the enzyme carbonic anhydrase and in the eye decreases the formation of aqueous humor.

Caruncle — A small fleshy eminence.

Catabolic — Destructive metabolism.

Cataract — An opacity of the lens.

incipient — Any cataract in its early stages, or one which has sectors of opacity with clear spaces intervening.

mature — One in which the lens is completely opaque and ready for operation.

hypermature — The lens has become either solid and shrunken or soft and liquid.

congenital — One which originates before birth.

senile — A hard opacity of the lens occurring in the aged.

traumatic — Cataract following an injury.

Choked disc — Swelling of the optic nerve.

Chorioretinitis — Inflammation of the choroid and retina.

Choroid — Vascular layer of the eyes—its function is to nourish the retina.

Ciliary body — Portion of vascular layer of eye whose function is secretion of aqueous humor.

Coloboma — A congenital defect in which a portion of a structure of the eye is absent.

Cone, retinal	Specialized visual cells in the retina, responsible for sharpness of vision and color vision.
Conical cornea, keratoconus	A conical protrusion of the cornea.
Conjunctiva	The delicate membrane that lines the eyelids and covers the exposed surface of the eyeball.
Contact lens, corneal	Contact lens molded for the cornea only.
Contact lens, scleral	Contact lens molded to the entire globe, not contacting the cornea.
Corticosteroids	Cortisone derivatives.
Cryosurgery	Use of low temperature in surgery.
Cup, optic	Depression in the center of the optic disc (nerve).
Cyclitis	Inflammation of the ciliary body.
Cycloplegia	Paralysis of the ciliary muscle.
Cytomegalic inclusion disease	Retinal viral inflammation.

D

Dacryocystitis	Inflammation of the lacrimal sac.
Demyelinizing	Loss of protective myelin sheath of nervous tissue; e.g., in multiple sclerosis.
Densitometry	Measurements of blood flow by determination of density of dyes introduced into the circulation.
Detachment of retina	A condition in which the inner layers of the retina are separated from the pigment layer.
Diathermy	Coagulation of tissue by heat such as used in retinal detachment surgery.
Diopter	A unit to designate the refractive power of a lens.
Diplopia	Double vision.
Disc, optic	The optic nerve as it enters the eye.

E

Electroretinogram	A record of the changes of potential in the retina after stimulation by light.
Emmetropia	Perfect vision.
Endophthalmitis	Inflammation of the internal structures of the eye.
Enucleation	Surgical removal of the eye.
Enzyme	An organic compound, frequently a protein, capable of accelerating or producing some change in another chemical compound for which it is often specific.
Esophoria	A tendency to deviation of a visual axis toward the other eye.
Esotropia	Actual deviation of the visual axis toward that of the other eye ("crossed eyes").
Etiology	The cause of a disease.
Exenteration	Surgical removal of the contents of a body cavity; e.g., the orbit.
Exophoria	A tendency to deviation of a visual axis away from that of the other eye when fusion is prevented.
Exophthalmos	Abnormal protrusion of the eyeball.
Exotropia	Deviation of a visual axis away from that of the other eye ("wall eye").
Extraction	The surgical removal of the lens; e.g., cataract removal.

F

Flash blindness	Visual disturbance resulting from intense light source; e.g., atomic bomb blast. It may be due to other forms of radiation as well.
Fluorescein	A fluorescent yellowish dye which is used in determining the fit of contact lenses or in the detection of corneal abrasions; also may be injected intravenously to study blood vessel pathology of the eye.
Fovea	A depression or pit in the center of the macula; it is the area of clearest vision.
Fundus	The interior of a hollow organ as the eye.

G

Geniculate body	A way station in the central nervous system for the transmission of visual impulses from the retina to the visual cortex of the brain.
Glaucoma	A condition of the eye characterized by increased intraocular pressure.
acute, closed angle	Glaucoma caused by obstruction of the filtration angle by the base of the iris.
chronic simple, open angle	Glaucoma in which the angle of the anterior chamber is open and free from obstruction.
congenital	Glaucoma present at birth due to a defect in the angle of the anterior chamber.
absolute	A final, hopeless stage in which vision is completely and permanently lost.
Glioma	A tumor derived from nerve tissue.
Gonioscopy	Examination of the anterior chamber of the eye.
Gonorrheal ophthalmia	Blinding eye disease of newborn infants acquired in the birth canal.

H

Hemianopia	Defective vision or blindness in half of the visual field.
Herpes simplex	An acute virus disease marked by groups of watery blisters on the skin and mucous membranes; the most common cause of blindness due to corneal disease.
Herpes zoster	An acute inflammatory disease affecting nerve tissue; shingles.
Heterograft	Transplant from one species; e.g., monkey, to another species; e.g., man.
Histoplasmosis	Parasitic inflammation affecting eye.
Homograft	Transplant from one member of a species; e.g., man to another member of the same species.
Hypermetrope	Farsightedness.
Hyphaema	Hemorrhage into the anterior chamber of the eye.
Hypophysectomy	Removal of pituitary gland.

I

IDU	Antimetabolic chemical agent, iododesoxyuridine, used as antiviral agent in ophthalmology.
Implant	An inert filler placed in the eyesocket after surgical enucleation.
Infrared heat scanning	Temperature sensitive techniques for diagnosis.
Intracapsular (adj.)	Removal of the lens with the lens capsule intact.
Intraocular pressure	The pressure of the fluid within the eye.
Iridectomy	Surgical removal of part of the iris.
Iridocyclitis	Inflammation of the iris and the ciliary body.

Iritis	Inflammation of the iris.
Ischemic	Lacking in blood.

K

Keratitis	Inflammation of the cornea; usually characterized by loss of transparency and dullness.
Keratoconus	Conical cornea, a conical protrusion of the cornea.
Keratoprosthesis	Corneal implant usually of plastic material, artificial cornea.

L

Lacrimal	Pertaining to the tears, or to the structure conducting or secreting tears.
Lagophthalmos	A condition in which the eye cannot be completely closed.
Lamellar	With reference to corneal transplant means removing partial thickness of cornea.
Lens	Lens of the eye: A transparent biconvex body, situated between the posterior chamber and the vitreous, through which the light rays are focused on the retina.
Lenticular (adj.)	Pertaining to or shaped like a lens.
Leukoma	A dense white opacity of the cornea.
Levator muscle	Muscle which raises the eyelid.
Limbus	A border; the edge of the cornea where it joins the sclera.

M

Macula	An oval area in the center of the retina devoid of blood vessels; most responsible for color vision.
Melanoma	A tumor arising from pigmented tissue (nevus).
Microphthalmos	A rare developmental defect in which the eyeballs are abnormally small.
Millimeter	One-tenth of a centimeter; 2.54 centimeters = 1 inch.
Miosis	Reduction in the size of the pupil.
Miotics	A drug which causes a reduction in the size of the pupil.
Muscae volitantes	Normal small floating spots seen when looking at a bright uniform field, such as the sky, attributed to minute remnants of embryonic structure in the vitreous humor.
Mydriasis	Increase in pupil size.
Myopia	Nearsightedness.
Myopic degeneration	A form of nearsightedness which may lead to blindness.

N

Needling (of cataract)	A surgical procedure in which the lens is punctured to allow the absorption of the lens substance.
Neuritis, optic	Inflammation of a nerve; e.g., the optic nerve.
retrobulbar	Inflammation of the orbital portion of the optic nerve.
Nucleus	A central mass, portion, or core.
Nystagmus	A regular, rapid, characteristically involuntary movement or rotation of the eye.

O

Oculist	An old term for ophthalmologist, still used in England.
Oculomotor (adj.)	Pertaining to the movements of the eye.
Onchocerciasis	Parasitic infection common in tropical areas.
Opacity	The condition of being opaque.
Ophthalmodynamometer	An instrument for measuring the blood pressure in the retinal artery.
Ophthalmologist	A medical practitioner specializing in the medical and surgical care of the eyes.
Ophthalmoscopy, direct	The observation of an upright mirrored image of the interior of the eye.
Ophthalmoscopy, indirect	The observation of an inverted image of the interior of the eye.
Optic atrophy	Degeneration of the optic nerve fibers; visual loss usually accompanies this condition.
Optic chiasm	An arrangement of nerve fibers in which the optic nerves of both eyes cross at a junction near the pituitary gland.
Optic disc	The portion of the optic nerve within the eye which is formed by the meeting of all the retinal nerve fibers at the level of the retina.
Optic neuritis	Inflammation of the optic nerve.
Optician	One who designs or manufactures optical instruments, including glasses.
Optometrist	An expert in optometry; nonmedical visual care.
Ora serrata	One of the sites of attachment of the retina to the choroid.
Orbicularis	An eyelid muscle which closes the eye.
Orbit	The cavity in the skull which contains the eyeball.
Orthoptics	The teaching and training process for the elimination of strabismus.

P

Pallor of disc	Paleness of the optic nerve, suggesting atrophy.
Palpebral (adj.)	Pertaining to an eyelid.
Palsy	Paralysis.
Panophthalmitis	Inflammation of all the structures of the eye.
Papilledema	Noninflammatory edema of the optic nerve head.
Paracentesis	Surgical puncture of a cavity for the aspiration of fluid; e.g., aspiration of aqueous humor.
Parasympathetic (adj.)	The nerve system which, in the eye, activates pupillary constriction.
Parasympathomimetic	A chemical agent that produces effects similar to those produced by stimulation of the parasympathetic nerves.
Paresis	Incomplete or partial paralysis.
Pathogenesis	Sequence of abnormal events causing a disease.
Pathway, visual	The neural path of visual impulses.
Pemphigus	A progressive and often fatal condition of blistering and scarring of the mucous membranes and the skin which can affect the eye.
Penetrating	With reference to corneal transplant means removing full-thickness corneal segment from epithelium to endothelium.
Perimeter	An instrument for measuring the field of vision.

Periphlebitis Inflammation of the tissues around a vein.

Phakoma A small grayish white tumor in the retina.

Phenothiazine A chemical compound forming the base of many currently used tranquilizers.

Phlyctenule A minute ulcerated nodule of the cornea or conjunctiva.

Phoria Any tendency to deviation of the eyes from normal.

Photophobia Abnormal sensitivity to and discomfort from light.

Phthisis bulbi Shrinking, wasting, and atrophy of the eyeball.

Pigment epithelium A layer of cells in the retina containing pigment granules.

Pilocarpine A substance that causes the pupil to contract.

Pituitary ablation Destruction of pituitary gland.

Pleoptics A technique of eye exercises designed to develop fuller vision and binocular cooperation.

Posterior pole of eye The center of the posterior curvature of the eyeball.

Presbyopia Impairment of vision due to advancing years or old age.

Prosthesis Artificial; e.g., eye.

Pterygium A growth of the conjunctiva considered to be due to a degenerative process caused by long continued irritation as from exposure to wind and dust.

Ptosis of the eyelid A paralytic drooping of the upper eyelid.

Pupil The opening at the center of the iris of the eye for the transmission of light.

Pyrogenic Producing temperature elevation.

R

Radiation, optic A structure in the brain made up of nerve fibers from the retina.

Rectus muscle A muscle attached to the eyeball which controls eye movements.

Reflex, corneal Blinking or winking in response to tactile stimulation of the cornea; reflection of light from the cornea.

Reflex, oculocardiac A slowing of the rhythm of the heart following compression of the eyes; if ocular compression produces acceleration of the heart, the reflex is called inverted.

Reflex, pupillary Constriction of the pupil when stimulated by light.

Refraction The determination of the refractive errors of the eye and their correction by glasses.

Refractive error A defect in the eye that prevents light waves from being brought to a single focus exactly on the retina.

Retina The innermost of the three tunics of the eyeball, surrounding the vitreous body and continuous, posteriorly, with the optic nerve.

Retinal correspondence Corresponding retinal areas in both eyes which perceive the same point in space simultaneously.

Retinal hole A space where the retina has pulled away from the underlying choroid tissue.

Retinitis pigmentosa An hereditary degeneration and atrophy of the retina.

Retinoblastoma A tumor arising from retinal germ cells; glioma of the retina.

Retino-choroiditis Inflammation of the retina and the choroid.

Retinopathy A disease of the retina due to various causes.

diabetic Changes in the retina due to diabetes mellitus.

hypertensive A disease of the retina associated with essential or malignant hypertension.

Retinoscope An instrument for measuring the refractive state of the eye.

Retrobulbar Situated or occurring behind the eyeball.

Retrolental fibroplasia A disease of the retina in which a mass of scar tissue forms in back of the lens; associated with premature birth and oxygen inhalation.

Rubeosis iridis Condition characterized by a new formulation of vessels and connective tissue on the surface of the iris.

S

Sac, conjunctival The potential space, lined by conjunctiva, between the eyelids and the eyeball.

Sac, lacrimal The dilated upper end of the nasolacrimal canal.

Sarcoidosis Disease of unknown cause affecting almost all systems of the body and frequently the eye.

Schlemm's canal A circular channel at the junction of the sclera and cornea through which aqueous humor leaves the eye.

Sclera The tough, white, protective coat of the eye.

Scotoma A blind or partially blind area in the visual field.

Screen, tangent A large square of black cloth, stretched on a frame, and having a central mark for fixation, used to map the field of vision.

Segment, anterior Referring to the front part of the eye.

Separation of retina Separation of the retina from its pigment epithelium layer.

Silicone Plastic available in solid or liquid form.

Slit lamp An instrument producing a slender beam of light for illuminating any reasonably transparent structure, as the cornea.

Spasm, lid (blepharospasm) A sudden, violent, involuntary contraction of the eyelid, attended by pain.

Spectrum, visible That portion of the entire spectrum which contains wavelengths capable of stimulating the retina.

Squint Strabismus.

Squint, accommodative That which is due to excessive or deficient accommodative effort.

convergent That in which the visual axes converge; cross eyed.

divergent That in which the visual axes diverge (exotropia).

paralytic Due to paralysis of an eye muscle.

Staphyloma Protrusion of the cornea or sclera resulting from inflammation.

Stereopsis Visual perception of depth or three-dimensional space.

Stereotactic surgery Use of three-dimensional localization in surgery.

Strabismus Squint; failure of the two eyes simultaneously to direct their gaze at the same object because of muscle imbalance.

Stye (hordeolum)	Inflammation of one or more of the sebaceous glands of the eyelids.
Subluxation	Incomplete dislocation of the lens.
Sympathetic ophthalmia	Inflammation of one eye due to an injury in the other eye.
Syndrome	A set of symptoms which occur together; a symptom complex.
Synechia	Adhesions, usually of the iris to the cornea or lens.

T

Tarsal plate	The framework of connective tissue which gives shape to the eyelid.
Tarsorrhaphy	Surgical attachment of upper and lower lids.
Tear film	Microscopic film which constantly bathes cornea.
Temporal (adj.)	Pertaining to the lateral region of the head.
Tenón's capsule	The fibrous membrane surrounding the sclera.
Test object	An object, pattern, or design used for vision testing.
Thromboendarterectomy	Surgical removal of clot from inner lining of blood vessel.
Tonography	The recording of changes in intraocular pressure produced by the constant application of a known weight on the globe of the eye.
Tonometer	An instrument for measuring the pressure inside the eye.
Toxoplasmosis	Infection with, or a condition produced by the presence of, organisms of the genus Toxoplasmosis.
TPI	Treponema pallidum immobilization test —for detection of syphilis.
Trachoma	A chronic, contagious, viral infection of the conjunctiva and the cornea.
Transillumination	The passage of light through body tissues for purposes of examination.
Tumbling (cataract)	Technique of removing cataract.

U

Ulcer, corneal	Pathological loss of substance of the surface of the cornea, due to progressive erosion and death of the tissues.
Ultrasound	Use of high-frequency sound waves—for diagnosis and treatment.
Uniocular (adj.)	Pertaining to or affecting but one eye.
Uveitis	Inflammation of the vascular coat of the eye (choroid, ciliary body, and the iris).

V

Vision, central	That which is elicited by stimuli impinging directly on the macula.
Vision, distant	Vision for objects at a distance (usually 20 feet or 6 meters).
Vision, near	Vision for objects at a distance corresponding to normal reading distance (13 to 16 inches).
Vision, peripheral	That which is elicited by stimuli falling on areas of the retina distant from the macula; i.e., side vision.
Vision, photopic	Vision attributed to cone function characterized by the ability to discriminate colors and small detail; daylight vision.
Vision, scotopic	Vision attributed to rod function characterized by the lack of ability to discriminate colors and small detail and effective primarily in the detection of movement and low-luminous intensities.
Visual acuity	Ability of the eye to perceive the shape of objects in the direct line of vision.
Visual axis	The line of gaze.
Visual cortex	Final station of visual impulses in the brain; sensory area of brain responsible for vision.
Visual field	The area of physical space visible to an eye in a given position.
Vitreous or vitreous body	Transparent, colorless mass of soft gelatinous material filling the eyeball behind the lens.

W

Water drinking test	Provocative test for glaucoma; the patient drinks 1 quart of water after fasting and the intraocular pressure is measured every 15 minutes.

X

Xerophthalmia	Conjunctivitis with atrophy and no liquid discharge which produces a dry, lusterless condition of the eyeball.

Z

Zonule of Zinn	The suspensory apparatus of the lens.
Zoster	An encircling structure.

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